IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,167,242

Patentee: Turner et al. Attn: Box Patent Extension

Issue date: December 1, 1992

Attorney Docket No.: A89675US

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REQUEST FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. § 156

Honorable Commissioner of Patents
and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Applicant, Pharmacia & Upjohn AB brings this Request For Extension Of Patent Term pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156.

Pharmacia & Upjohn AB, a corporation registered in Stockholm, Sweden, is the assignee and owner of the entire interest in and to U.S. Patent Number 5,167,242. Pharmacia & Upjohn's ownership of the patent is established by virtue of an assignment from the inventors to Pharmacia Aktiebolag, recorded July 31, 1990, in Reel 5388, Frames 0657-0674; as well as a name change document from Pharmacia AB to Pharmacia Aktiebolag recorded on October 28, 1991, at Reel 5941, Frames 0505-0515; and the following name change documents, filed herewith for recordation with the U.S. Patent and

Trademark Office attached to Exhibit 1 (Power of Attorney) for Patent Number 5,167,242:

(i) A Swedish Certificate Of Registration (Registration No. 556029-7094) (one page) indicating that on 29th April, 1994 the Court gate its permission for the fusion of Kabi Pharmacia Aktiebolag ("AB") ("AB" is an abbreviation of Aktiebolag) to Pharmacia AB and thus the change in name of the owner of the 5,162,242 patent from Kabi Pharmacia Aktiebolag to Pharmacia AB became effective on April 29, 1994;

(ii) A Swedish Certificate Of Registration (Registration No. 556131-9608) (one page) indicating that on July 1, 1996 (1996-07-01) the owner of the 5,167,242 patent, Pharmacia AB, changed its name to its current name, Pharmacia & Upjohn AB.

This application is being submitted by Pharmacia & Upjohn AB's authorized agent as set forth in 37 C.F.R. §1.730 (see Exhibit 1 for a copy of the Power of Attorney authorizing the undersigned to act in this manner).

Applicant hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. 1.740 and follow the numerical format set forth in 37 C.F.R. § 1.740.

(a)(1) A complete identification of the approved product as

by appropriate chemical and generic name, physical structure or characteristics:

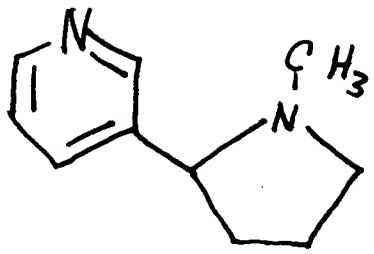
The approved product is the Nicotrol® Inhaler (nicotine inhalation system), 10 mg/cartridge (4 mg delivered). The approved product contains GASEOUS / VAPOR PHASE NICOTINE as the active ingredient.

The approved product is fully described in the attached Draft Product Insert which has been approved by the FDA for the product and is attached hereto as Exhibit 2, which Exhibit is hereby incorporated herein by reference in its entirety.

Briefly, the approved Nicotrol® Inhaler product (nicotine inhalation system) consists of a mouthpiece and a plastic cartridge delivering 4 mg of gaseous nicotine from a porus plug containing 10 mg nicotine. The cartridge is inserted into the mouthpiece prior to use.

Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, freely water-soluble, strongly alkaline, oily, volatile, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic pungent odor and turns brown on exposure to air of light. Of its two stereoisomers, S(-)nicotine is the more active. It is the prevalent form in tobacco, and is the form in the Nicotrol® Inhaler. The free alkaloid is absorbed rapidly through the skin, mucous membranes, and respiratory tract.

The structural formula of nicotine is:



The chemical name is S-3-(1-methyl-2-pyrrolidinyl)pyridine. The molecular formula is $C_{10}H_{14}N_2$. The molecular weight is 162.23. The ionization constants are pKa_1 = 7.84 and pKa_2 = 3.04 at 15 C. Its octanol-water partition coefficient is 15:1 at pH 7.

Nicotine gas/vapor is the active ingredient of the product. Inactive components of the product are menthol and a porous plug which are pharmacologically inactive. Nicotine gas is the ingredient that is active when the drug of the product is administered to a patient, nicotine vapor being released from the inhaler and delivered to the patient when the patient inhales through the inhaler.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review period occurred.

The regulatory review occurred under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

Applicant respectfully submits that, as explained in section 13(b) herein and as supported by the accompanying Declaration by Mr. Anders Sjöholom (attached hereto as Exhibit 3), applicant believes and asserts that the date on which the Nicotrol® Inhaler product first received final, non-conditional permission from the FDA for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred was September 24, 1997.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that is has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) the use for which it was approved, and the provision of law under which it was approved.

Applicant respectfully submits that, as explained in section 13(a) herein and as supported by the accompanying Declaration by

Sven-Börje Andersson (attached hereto as Exhibit 4), applicant believes and asserts that the active ingredient of the instant product, VAPOR PHASE NICOTINE, has not previously been approved for commercial marketing or use under any Federal statute that applicants are aware of.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last date on which the application could be submitted.

As indicated above, applicants submit that the product was finally approved by the FDA for final non-conditional commercial marketing or use on September 24, 1997. This application is being submitted on November 21, 1997. The date of the last date on which an application could be submitted is November 22, 1997. Therefore, applicants submit, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

U.S. Patent Number 5,167,242

Inventors: James E. Turner, Michael P. Ellis, Ronald G. Oldham, Ira Hill, Bengt E. Malmborg, and Sven-Böje Andersson

Issued: December 1, 1992

Expires: June 8, 2010 (20 years from date of filing)

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawing.

A complete copy of U.S. Patent No. 5,167,242 is attached hereto as Exhibit 5.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issue in the patent.

A copy of the receipt for the first maintenance fee payment paid by applicant is attached hereto as Exhibit 6. Said receipt has a Patent Office receipt date of May 20, 1996.

No disclaimer, certificate of correction, or reexamination certificate has been issued in connection with U.S. Patent No. 5,167,242.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product.

U.S. Patent Number 5,167,242 claims the approved product. The approved Nicotrol® Inhaler product is described on the attached FDA-approved draft product insert attached hereto as Exhibit 2, which is hereby incorporated by reference in its entirety. Each claim of the 5,167,242 patent reads upon the approved product.

Claim 1

A cartridge for a nicotine inhaler, comprising:

a) a cartridge housing;

b) a passageway in said cartridge housing;

c) a nicotine reservoir in said passageway for holding a measured amount of nicotine in a form that will allow nicotine vapor to be released into a fluid stream passing around or through the reservoir;

d) said passageway comprising at least two openings communicating outside said housing for allowing a fluid stream to pass through said passageway;

e) said nicotine reservoir being sealed from the atmosphere and maintained in an effectively oxygen-free environment by a nicotine-impermeable barrier which includes passageway barrier portions for sealing the passageway on both sides of the reservoir, at least one said passageway barrier portions being penetrable for opening said passageway to the atmosphere; and

f) said passageway further having a portion inside said passageway barrier portion that is filled with inert gas.

Claim 2

The cartridge of claim 1, wherein the cartridge housing is an

elongated member, the passageway being defined by the inner surface on the member and the passageway openings being located on opposite ends of the member.

Claim 3

The cartridge of claim 2, wherein the elongated member is cylindrical in shape.

Claim 4

The cartridge of claim 2 in combination with a mouthpiece, said mouthpiece comprising:

a) an elongated passageway section with openings at both ends;

b) one end of the passageway section adapted to be received in the mouth of the user;

c) the other end of the passageway section having an inner surface adapted to receive and hold said cartridge housing within the passageway section, and the mouthpiece, passageway section and cartridge communicating with each other; and

d) said other end of the passageway section includes a sharpened end around the periphery for penetrating said penetrable passageway barrier portions.

Claim 5

The cartridge of claim 4 in combination with a dispenser, said dispenser comprising:

a) a molded plastic dispenser containing a number of compartments and a tray;

b) said compartments are adapted to accommodate cartridges;

c) said tray is adapted to accommodate a mouthpiece; and

d) a sharpened tip, for penetrating the penetrable passageway barrier portions, is located at one end of the tray.

Claim 6

The cartridge of claim 1, wherein the nicotine reservoir comprises a porous polymer plug charged with nicotine free base.

Claim 7

The cartridge of claim 6, wherein the porous plug is formed of polyethylene.

Claim 8

The cartridge of claim 1, wherein said housing is formed of a copolymer of acrylonitrile and methyl acrylate.

Claim 9

The cartridge of claim 8 wherein the nicotine-impermeable barrier includes forming the passageway barrier portions of aluminum foil.

Claim 10

The cartridge of claim 9, wherein the aluminum foil includes a coating on at least one side of a copolymer of acrylonitrile and methyl acrylate with said coating being heat sealed to the housing.

Claim 11

The cartridge of claim 1, wherein said cartridge housing is covered with a layer of aluminum foil.

Claim 12

The cartridge of claim 11, wherein the aluminum foil includes a coating on at least one side of a copolymer of acrylonitrile and

methyl acrylate with said coating being heat sealed to the housing.

Claim 13

The cartridge of claim 1, wherein said inert gas is nitrogen.

Claim 14

A nicotine delivery system with an extended shelf life, containing a measured amount of nicotine which can selectively be made accessible to a user, comprising:

a) a container formed of a material which is effectively impermeable to nicotine and oxygen;

b) a carrier in the container for carrying a measured amount of nicotine in a state which can supply nicotine in vapor form to a user, said carrier being maintained in the container in an effectively oxygen-free environment;

c) access means for selectively providing the user with access to the interior of the container; and

d) differential pressure means for allowing a differential pressure to be applied to the carrier for releasing nicotine in vapor form through said access means when the interior of the container is made accessible to the user.

Claim 15

The nicotine delivery system of claim 14, wherein the nicotine carrier comprises a porous polymer plug charged with a nicotine free-base.

Claim 16

The nicotine delivery system of claim 15, wherein the porous plug is formed of polyethylene.

Claim 17

The nicotine delivery system of claim 14, wherein said access means includes a selectively penetrable portion attached to the carrier by means of a nicotine-impermeable seal.

Claim 18

The nicotine delivery system of claim 14, wherein the container is tubular in shape and said access means and said differential pressure means includes penetrable seals at opposite ends of the container.

Claim 19

The nicotine delivery system of claim 14, wherein the container is formed at least in part of a polymer of acrylonitrile and methyl acrylate.

Claim 20

The nicotine delivery system of claim 19, wherein said access means is formed of an aluminum foil coated with a copolymer of acrylonitrile and methyl acrylate.

Claim 21

The nicotine delivery system of claim 20, wherein the coating of copolymer of acrylonitrile and methyl acrylate is heat sealed to the container.

Claim 22

The nicotine delivery system of claim 14, wherein the carrier is maintained in inert gas.

Claim 23

The nicotine delivery system of claim 22, wherein said inert

gas is nitrogen.

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) was initially submitted and the NDA number and the date on which the NDA was approved.

On July 10, 1990, Pharmacia AB (parent company to Pharmacia & Upjohn AB) submitted to the U.S. Food and Drug Administration ("FDA") a "Notice of Claimed Investigational Exemption for a New Drug" (hereinafter referred to as an "IND") for its Nicotrol® Inhaler product. The submission was received by the FDA on July 16, 1990. The IND became effective thirty days after receipt of the IND by the FDA, which was August 15, 1990, and was assigned number 35,105. These facts are confirmed in a letter from the FDA to Pharmacia Inc. dated July 18, 1990. A copy of this letter is attached as Exhibit 7. Several supplements thereto have been filed. This establishes the beginning of the "regulatory review period" under 35 U.S.C. § 156(g)(1) as August 15, 1990.

On May 1, 1996, a New Drug Application ("NDA") for the Nicotrol® Inhaler product was submitted to the FDA under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") and

was assigned number 20-714. These facts are confirmed in a letter from the FDA to Pharmacia Inc. dated May 15, 1996. A copy of this letter is attached as Exhibit 8. Two supplements were filed to this NDA, Supplement 001 was filed as a Supplemental New Drug Application ("SNDA") with the FDA on July 15, 1997, covering new child-resistant features of the Nicotrol® Inhaler product and new labeling. Supplement 002 was filed with the FDA on July 15, 1997 as a Changes Being Effected Supplement and covered a sampling program to physicians. A FDA letter regarding the NDA was mailed to Pharmacia & Upjohn Company on May 2 1997 (copy attached as Exhibit 9). However, as discussed in section 13(b) herein, as well as the attached Declaration by Anders Sjöholom (attached hereto as Exhibit 3), applicants believe and assert that the May 2 1997 FDA letter was NOT a "final approval" letter for final, unconditional commercial marketing or use of the Nicotrol® Inhaler product covered by the NDA. Rather, applicants believe and assert that final, non-conditional approval by the FDA for commercial marketing or use of the Nicotrol® Inhaler product covered by the NDA was given by the FDA in an approval letter for the modified, child-resistant product covered in the 001 SNDA. This letter was mailed on September 24, 1997 (copy attached hereto as Exhibit 10). The 002 Changes Being Effected Supplement was approved by the FDA on October 29, 1997.

Thus, applicants assert, for purposes of determining the "regulatory review period" under 35 U.S.C. § 156(g)(1), the date of first final FDA approval for commercial marketing or use of the

Nicotrol® Inhaler product in the United States is September 24, 1997.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities are summarized below as well as in the attached Exhibit 17, Declaration By Lars Nilsson, Vice President for Regulatory and Quality Affairs at Pharmacia & Upjohn AB.

ACTIVITIES DURING THE REGULATORY REVIEW PERIOD

Date	Activity
Study Period: Oct. 1990- Jan. 1992	Clinical study T90NI03 ongoing. Protocol May 1990. Report Feb. 1996
Study period: Nov. 1990 - Apr. 1992	Clinical study T90NI02 ongoing, Protocol Jun. 1990. Report Feb. 1996
Study period: Oct. 1990 - Nov. 1992	Clinical study T90NI01 ongoing. Protocol Jun. 1990. Report Feb. 1996
Study period: Sept. 1991 analytical test: Oct.-Nov. 1991	Pharmacokinetic study T91NI05, Report Dec. 1992
Study period: Oct. - Nov. 1991, analytical tests: Jan. - Feb. 1992	Pharmacokinetic study T91NI06, Prel. report Feb. 1992 Re-evaluation 1996. Report

Jun. 1996	
Study period: Oct. 1991 - Feb. 1992, analytical tests: May - Jun. 1992	Pharmacokinetic (pilot) study T91NI07, Report Nov. 1993
Study period: May - Jun. 1992, analytical tests: Aug. - Sep. 1992	Pharmacodynamic study 92NNIN004. Protocol Mar. 1992. Report Jul 1993
Jul. 1, 1992	**IND Submission**; Protocol 92NNIN002
Sep. 16, 1992	IND Submission; Protocol 92NNIN003
Study period: Sep. - Oct. 1992, analytical tests: Dec. 1992	Pharmacokinetic study 92NNIN005. Prel. report Dec. 1993. Re-evaluation 1994. Report Apr. 1995.
Nov. 16, 1992	Submission of Annual Report
Dec. 1, 1992	IND Submission; Protocol T91NI04
Study period: Oct. 1992-June 1994	Clinical study T91NI04 ongoing. Report Feb. 1996
Study period: May - Dec. 1993	Pharmacokinetic study 93NNIN007. Protocol Mar. 1993. Report Mar. 1994
Study period: Dec. 1994	Addendum to Pharmacokinetic study 93NNIN007. Protocol Sep. 1994. Report Jun. 1995
Study period: I: Feb. - Jun. 1995 and II: Mar. - Apr. 1996	Pharmacokinetic study 94 NNIN010, Protocol Dec. 1994. Report Feb. 1997 (I+II) (preliminary report Jan. 1996, I)
Study period: May-Jun. 1995, analytical tests: Jul.- Aug.	Pharmacokinetic study 95NNIN011, Report Dec. 1995
1995	
Sep. - Oct. 1995	Pharmacokinetic study 95NNINI013, Report 1996 (Japan)

Re-evaluation: Dec. 1995- Jan. 1996	Report of re-evaluated pharmacokinetic pilot study T88NI02
1995 - Aug. 1996	Plans for and installation, qualification and validation of full scale production equipment and process
Jan. 1996 - Apr. 1996	Clinical summaries
Mar. 1996 - Apr. 1996	Compilation of NDA
May 1, 1996	**Submission of NDA**
Jun. 5, 1996	Submission of prototype mouthpiece
Jun. 13, 1996	Submission of requested documentation
Jun. 18, 1996	Telephone conference with the FDA
Jun. 24, 1996	Submission of requested data
Jul. 8, 1996	Questions from the FDA
Aug. 19, 1996	Submission of electronic versions of physician package insert and patient package insert August 19, 1996
Aug. 1996 to date	Plans for and installation, qualification and validation of new full scale production equipment
Sep. 6, 1996	Responses to questions of Jul. 8, 1996
Sep. 27, 1996	Submission of requested extra copies of clinical study reports
Oct. 31, 1996	Submission of Draft Advisory Committee Brochure
Nov. 6, 1996	Submission of publicly releasable version of Environmental Assessment Report

Nov. 8, 1996	Meeting with the FDA to finalize the Advisory Committee Brochure
Nov. 15, 1996	Submission of background material for the Nicotrol Inhaler Drug Abuse Advisory
Nov. 22, 1996	Request for more information
Dec. 5, 1996	Submission of NDA Amendment
Dec. 13, 1997	DAAC (Drug Abuse Advisory Committee) meeting with FDA
Jan. 13, 1997	Submission of responses to FDA's questions
Jan. 29, 1997	Supplemental responses
Feb. 7, 1997	Methods Validation Package to FDA laboratories
Mar. 6, 1997	Questions from the FDA
Mar. 7, 1997	Submission of NDA Amendment
March 10, 1997	Submission of revised methods to FDA laboratories
Mar. 20, 1997	Submission of Revised Draft labelling
Mar. 24, 1997	Submission of Responses
Mar. 26, 1997	Revised patient information leaflet
Mar. 31, 1997	Submission of requested analytical equipment to FDA laboratories
April 4, 1997	Submission of requested analytical equipment to FDA laboratories
Apr. 7, 1997	Responses to questions submission of requested document clinical study report

Apr. 15, 1997	Submission of Development plan
Apr. 24, 1997	Revised draft label
May 1, 1997	Submission of Phase IV Commitments
May 2, 1997	Letter from FDA
May 5, 1997	Submission of requested additional samples to FDA
May 5 - July 15, 1997	Ongoing development of child resistant mouthpiece and minor corrections of appearance
July 5, 1997	Submission of supplemental information
July 23, 1997	Response to FDA request of July 15, 1997
September 4, 1997	Submission of child resistant test results to FDA
September 4, 1997	Submission of responses to questions
September 24, 1997	**FDA final approval letter**

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

(A) Statement of eligibility of the patent for extension under 35 U.S.C. § 156(a):

Applicant is of the opinion that U.S. Patent No. 5,167,242 "'242") is eligible for extension under 35 U.S.C. § 156 because it satisfies all the requirements for such extension as follows:

(a) 35 U.S.C. § 156(a)

The '242 patent claims an FDA-approved product, the Nicotrol® Inhaler product.

(b) 35 U.S.C. § 156(a)(1)

The term of the '242 patent (June 8, 2010) has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2)

The term of the '242 patent has never been extended.

(d) 35 U.S.C. § 156(a)(3)

This application is being submitted by an authorized agent of the owner of record of the subject patent. The appropriate Power Of Attorney and proof of ownership of the '242 patent is shown in the attached Exhibit 1.

(e) 35 U.S.C. § 156(a)(4)

The Nicotrol® Inhaler product has been subject to a regulatory review period before its commercial marketing or use. The product was reviewed under Section 505(b) of the FFDCA before its commercial marketing or use, as is evidenced from the FDA letters attached hereto as Exhibits 7-10.

(f) 35 U.S.C. § 156(a)(5)(A)

Applicant believes and submits that the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the active ingredient of the product under the provision of law under which such regulatory review period occurred. This position is further explained in section 13(b) herein as well as in the attached Declaration by Anders Sjöholom attached hereto as Exhibit 3.

(B) Statement as to the length of extension claimed:

The term of Patent No. 5,167,242 should be extended by, applicants believe, 473 days. This term of extension was determined on the following basis. As set forth in 35 U.S.C. § 156(g)(1)(B), the regulatory review period for a new drug equals:

(i) the period beginning on the date an exemption under subsection (i) of Section 505 or subsection (d) of Section 507 became effect for the approved product and ending on the date an application was initially submitted for such drug product under section 351, 505, or 507, and

(ii) the period beginning on the date the application was initially submitted for the approved product under section 351, subsection (b) of section 505, or section 507 and ending on the date such application was approved under such section.

The regulatory review period thus equals the length of time between the effective date of the initial IND (August 15, 1990, in this case), and the initial submission of the NDA (May 1, 1996, in this case), a period of, applicants believe, 2084 days, plus the length of time between the initial submission of the NDA (May 1, 1996) and final unconditional approval of the NDA (September 24, 1997, in this case), a period of, applicants believe, 512 days. Making the total regulatory review period under section 156(g)(1)(B), applicants believe, 2596 days.

In accordance with 35 U.S.C. § 156(c), the term of a patent eligible for extension under subsection (a) shall be extended by the time equal to the regulatory review period for the approved product of which period occurs after the date the patent is issued, except that each period of the regulatory review period shall be reduced by any period determined under subsection (d)(2)(B) during which the applicant for the patent extension did not act with due diligence during such period of the regulatory period and the period of extension shall include only one-half of the time remaining in period described in paragraph (1)(B)(i) (the time between the effective date of the IND and submission of the NDA).

Further, 35 U.S.C. § 156(c)(3) indicates that "if the period remaining in the term after the date of the approval of the approved product under the provision of law under which such regulatory review occurred when added to the regulatory review period exceeds fourteen years, the period of extension shall be reduced so that the total of both sections does not exceed fourteen years."

The extension for U.S. Patent Number 5,167,242 thus equals one-half the period described in paragraph (1)(B)(i) (the time between the effective date of the IND and submission of the NDA), beginning after the date the patent issued, thus, beginning on December 1, 1992 (In this case, this period is thus, applicants believe, 624 days, being one-half the number of days from December 1, 1992 (date of issuance of the patent) to May 1, 1996 (date of submission of the NDA) (1248 days, applicants believe, one-half being, applicants believe, 624)) plus the period described in paragraph (1)(B)(ii) (the time between the date of submission of the NDA and final FDA approval of the NDA), in this case, applicants believe, 512 days. No period shall be reduced due to lack of due diligence, since there has been no lack of due diligence during the regulatory review period.

This means that the regulatory review period as revised under 35 U.S.C. § 156(c)(1)-(2), applicants believe, is 1136 days. However, when this revised regulatory review period (1136 days) is added to period of time remaining in the term of the patent after

final FDA approval of the product (which applicants believe is 4637 days, the period from September 25, 1997 (the day after the FDA approval date) to June 8, 2010 (original expiration date)), as required under 35 U.S.C. § 156(c)(3), the total (5773 days) exceeds 14 years. Therefore, under section 156(c)(3) the period of extension shall be reduced to not exceed 14 years from the date of final FDA allowance. In this case, therefore, applicants believe, the 5,167,242 patent shall expire on September 24, 2011, making the period of patent term extension 473 days (running from June 9, 2010 to September 24, 2011).

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services of the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicant and applicant's attorney acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services of the Secretary of Agriculture under 37 C.F.R. § 1.765 any information which is material to the determination of the extension sought herein.

In accordance with this duty, applicant wishes to make of record the following information:

(A) Information concerning the "active ingredient" of the product

Applicant specifically calls the Commissioner's attention to Exhibit 4, attached hereto and incorporated by reference herein, which is a Declaration by Sven-Börje Andersson regarding the "active ingredient" issue.

As sworn to in the attached Andersson Declaration, applicant believes, and asserts, that the recent FDA approval of the subject Nicotrol® Inhaler was the first FDA approval of the "active ingredient" of the product.

Applicant acknowledges and understands that patent term extension is only available under 35 U.S.C. § 156 following the first FDA approval of the active ingredient of a drug product. However, applicant believes and asserts that the recent FDA approval of the Nicotrol® Inhaler represents, in fact, the first FDA approval of the active ingredient of the product, which is VAPOR PHASE NICOTINE.

(a) The active ingredient delivered from the Nicotrol® Inhaler upon administration of the drug product is VAPOR PHASE NICOTINE

Applicant notes that the active ingredient delivered from the Nicotrol® Inhaler upon administration of the drug product is the evaporable "free-base nicotine" which is delivered as VAPOR PHASE

NICOTINE (i.e., nicotine in its gaseous form). Applicant recognizes and notes that under *Glaxco Operations UK Ltd. v. Quigg*, 13 USPQ2d 1628 (Fed. Cir. 1990) (copy attached to Mr. Andersson's Declaration in Exhibit 4) the term "active ingredient" in 35 U.S.C. § 156 means the active ingredient of the drug when administered.

The delivered (administered) active ingredient of the Nicotrol® Inhaler is VAPOR PHASE NICOTINE. This is because in administration of the active ingredient to the patient, it is solely GASEOUS NICOTINE that is inhaled from the inhaler by the patient. While the pre-used inhaler contains nicotine associated with a porous plug, as indicated on page 1 of the FDA-approved Nicotrol® Inhaler Draft Product Insert (see Exhibit 2), when the product is administered, the *active* ingredient "[n]icotine is released when air is inhaled through the Inhaler." It is *only* VAPOR PHASE NICOTINE that is *administered* from the product to the patient (i.e., the nicotine associated with the plug must first be volatilized in order to be sucked as a vapor from the device by the patient and administered to the patient as a vapor by inhalation). Hence, it is clear that the *active* ingredient of the Nicotrol® Inhaler when the product is *administered* is VAPOR PHASE NICOTINE.

Indeed, applicant notes that this position is both consistent with and encouraged by the Federal Circuit's interpretation of Section 156(f)(2) in *Glaxco Operations UK Ltd. v. Quigg*, 13 USPQ2d 1628 (Fed. Cir. 1990) (a copy of which is attached to Mr. Andersson's Declaration). In that case the Federal Circuit held that the term "active ingredient" in 35 U.S.C. § 156(f)(2) is

unquestionably to be construed quite narrowly to encompass ONLY three specific categories -- i) exactly the same active ingredient of the product, *when the product is administered*, or ii) the salt, or iii) the ester of exactly the same active ingredient, *when the product is administered*. The Court was clear in mandating that the Commissioner is quite restricted in determining what "products" have been previously first approved by the FDA on the basis of their "active ingredients," -- mandating that the Commissioner only reject extension applications where the "*active* ingredient" of a drug when (and only when) the drug is *administered* is exactly the same active ingredient (or a salt or ester of exactly the same active ingredient), *when the product is administered*.

The Court insisted that all other cases but for these restricted and precise few will necessarily fall outside the definition of previous first approval and thus not be barred by prior first FDA approval of, for example, a merely related compound. See, for example, 13 USPQ2d at 1633:

> In the instant case [that of the meaning of "active ingredient" under Section 156], Congress qualified its express authorization to the Commissioner to determine whether patents are eligible for extension...by providing an explicit and precise definition of "product" in section 156(f)(2), using well-established scientific terms. Although the definition does involve technical subject matter, Congress specifically selected terms with narrow meanings that it chose from among many alternatives. Congress could have, but did not, select broad terms with a range of possible meanings. If it had, Congress could be said to have implicitly delegated discretion to the Commissioner to use his scientific expertise to determine what further definition would best carry out the purpose of the Act. Here, all Congress left to the Commissioner's technical expertise was determining *whether* any patented chemical compound named

in a patent term extension application fell within the statutory definition of "product," but *not what* "product" was to mean.

Glaxco Operations UK Ltd., 13 USPQ2d at 1633 (italics in original, underlining and bold added).

Hence, applicant submits, it is clear here that under the Federal Circuit's mandated narrow definition of the same "active ingredient" of a drug product, in the present case, the active ingredient of the nicotine inhaler, GASEOUS NICOTINE does NOT fall within the narrow definition of Section 156(f)(2) -- it is NOT exactly the same active ingredient at the time of administration (or a salt or ester thereof) as any "active ingredient" upon administration of any previously approved nicotine-related drug product. The exact ingredient that is "active" at the exact time of administration of the Nicotrol® Inhaler, GASEOUS NICOTINE, is not exactly the same as that of any previously approved use related to nicotine.

(b) Prior FDA approvals related to nicotine delivery products did not approve the present active ingredient, NICOTINE VAPOR

As indicated in the attached Declaration by Mr. Andersson, applicant is aware of earlier FDA approvals of other active ingredients associated with nicotine delivery products, but none which concern the delivery of NICOTINE VAPOR as the active ingredient.

Specifically, applicant understands that on January 13, 1984,

Merrell Dow received FDA approval for Nicorette® nicotine-containing chewing gum. However, the active ingredient of this product was not NICOTINE VAPOR. Rather, applicant understands that the registered drug substance was "nicotine polacrilex." Applicant understands that nicotine was present in an ion-exchange complex; the nicotine was only released when the gum was actively chewed (i.e., if the gum just resided in the mouth, no nicotine would be administered); and that administration was to the mucosa in the mouth.

Applicant, Pharmacia & Upjohn AB, had experience with FDA approval of its Nicotrol® - nicotine transdermal system, which approval occurred on April 22, 1992. In that product, the nicotine was present, and administered to the patient in a liquid state via transdermal administration, the delivery being controlled through diffusion in the adhesive of the patch.

Applicant has also had experience with FDA approval of its Nicotrol® - nicotine nasal spray. On March 22, 1996 the FDA approved this product having as its active ingredient diluted liquid phase nicotine, being administered in droplet (microdroplet) form to the nasal mucosa.

However, none of the FDA approvals that applicant is aware of have approved VAPOR PHASE NICOTINE as the active ingredient of any drug product.

Unlike the other FDA approvals of any other nicotine-related products that applicant is aware of, the vapor phase product is unique in at least the way that it administers its unique active

ingredient at the time of administration since, in at least some extent it mimics actual cigarette smoking, taking into account the behavioral nature of smoking (hand movement to the lips and inhalation or puffing), but distinct from the inhalation of harmful cigarette smoke into the lungs.

In further support of applicant's assertion that the FDA-approved active ingredient of the Nicotrol® Inhaler, VAPOR PHASE NICOTINE, is a separate active ingredient from anything previously approved by the FDA, applicants note that the Concise® Oxford Dictionary defines "VAPOR" as a unique medicinal agent for inhaling ("Vapor:...**a medicinal agent for inhaling**" see attachment to Exhibit 4). As attested to in the attached Declaration by Mr. Andersson, and as agreed to and asserted to herein by applicant, this commonly accepted definition of "VAPOR" as a distinct medicinal agent further, and clearly, distinguishes -- AS A DIFFERENT AND DISTINCT ACTIVE INGREDIENT -- the use (administration) of a VAPOR as the active ingredient from, for example, the use (administration) of any other form(s) of a compound.

In summary, applicant believes that it is quite reasonable to say that the "active ingredient" (especially as defined by the *Glaxco Operations UK Ltd.* case as being the ingredient of the drug which is active when the drug is administered) of the Nicotrol® Inhaler is VAPOR PHASE NICOTINE and as such, and under the teaching of *Glaxco Operations*, is a different active ingredient from that of any other forms of nicotine that have previously been approved by

the FDA.

(B) Information concerning the timing of the "final" FDA approval of the product

Applicant specifically calls the Commissioner's attention to Exhibit 3, attached hereto and incorporated by reference herein, which is a Declaration by Anders Sjöholom regarding the issue of the timing of the FDA's "final," nonconditional approval for commercial marketing or use of the Nicotrol® Inhaler product in the United States.

As sworn to in the attached Sjöholom Declaration, and agreed with by applicant, applicant believes, and asserts, that the September 24, 1997 FDA approval letter of the subject Nicotrol® Inhaler was the first "final" and non-conditional FDA approval for marketing or use of the inhaler product, thereby causing the 60 day time period of Section 156(d)(1) to run from September 24, 1997, thereby rendering this application timely.

Applicant's position on this matter, as noted in more detail on the attached Declaration by Sjöholom of which applicant agrees in full, is fully consistent with, indeed encouraged by, the three U.S. court cases, which applicants are aware of, which have addressed the issue of what exactly constitutes "final approval" for commercial marketing and use under 35 U.S.C. § 156(d). Specifically, applicants refer to *Unimed, Inc. V. Quigg*, 12 U.S.P.Q.2d 1644 (Fed. Cir. 1989); *Mead Johnson Pharmaceutical Group*

v Bowen, 6 USPQ2d 1565 (D.C.Cir. 1988); and *Norwich Eaton Pharmaceuticals, Inc. v. Bowen*, 808 F.2d 486 (6th Cir. 1987) (copies of these cases are attached accompanying the Declaration by Sjöholom, as Exhibit 3).

Applicant notes that in the *Mead Johnson* and *Norwich Eaton* cases, the courts held that for purposes of the transitional provisions of the Patent Term Extension Act, the date when a new drug is "approved" by the FDA is the date of the FDA approval letter, even where the applicant still needs to submit final printed labeling to the FDA. (See 12 U.S.P.Q.2d 1644, at 1646). However, applicant asserts, the situation with the nicotine inhaler is clearly different from those cases. Here, the FDA is not merely reminding the applicant of the of formal follow-up matters that are not a precondition to final full approval of marketing or use (such as submission of the final printed label).

Rather, in this case, the FDA's letter of May 2, 1997 clearly stated a PRECONDITION for final, non-conditional full FDA approval for commercial marketing or use of Pharmacia & Upjohn's Nicotrol® Inhaler. As clearly indicated on the second page of the May 2, 1997 letter (attached hereto as Exhibit 9), Pharmacia & Upjohn was required ("committed") to modify the inhaler product to become child resistant within 6-12 months of May 2, 1997. Applicants submit that this FDA requirement is squarely different from the labeling requirement addressed in the previous cases. Applicant agrees that the FDA "requirement" that the final labeling be submitted following approval does not constitute a "precondition"

to "final approval" to commercialize the product, and is thus not a bar to effective "final approval" under Section 156(d). However, applicant believes that the FDA's requirement that Pharmacia and Upjohn modify their nicotine inhaler to become child resistant within 6-12 months of May 2, 1997 does, in fact, constitute a *de facto* bar BY THE FDA to final unrestricted, unconditional "approval" to market the product. It is, in short, not a "final" approval as envisioned by Section 156(d) and the U.S. courts.

We believe this at least because in order to satisfy this requirement, another New Drug Application was required to be submitted, reviewed and approved by the FDA covering the modified, child proof inhaler, before the FDA would grant "final" unrestricted, unconditional approval for Pharmacia & Upjohn to market or use its Nicotrol® Inhaler in the United States. This is borne out by the fact that in response to the letter of May 2, 1997 -- rather than commercializing a product -- instead Pharmacia & Upjohn was required by the FDA to submit a supplemental new drug application covering its modified Nicotrol® Inhaler, which had been modified to become child-resistant at the insistence of the FDA (see attached Declaration by Sjöholom, the supplemental NDA covering the child-resistant inhaler was filed with the FDA on July 15, 1997).

Hence, applicant respectfully submits, and as sworn to in the attached Declaration of Sjöholom, unlike the FDA letters addressed in the *Mead Johnson* and *Norwich Eaton* cases, the instant FDA letter of May 2, 1997 was not, in fact, a "final" approval to Pharmacia &

Upjohn market or use its nicotine inhaler product in the U.S. -- rather, it was a conditional, non-final letter, with full, final marketing approval conditioned upon the FDA subsequently approving a child proof product, such approval being a prerequisite to full, final unconditional FDA approval to market or use the Nicotrol® Inhaler in the U.S.

Next, and importantly, applicant believes that the facts in the present case are readily distinguished from those considered by the Federal Circuit in *Unimed, Inc. V. Quigg.* Indeed, applicant submits that viewing the present facts in light of the Federal Circuit's teaching in *Unimed* mandates for a conclusion that the May 2, 1997 FDA letter does not qualify as the Nicotrol® Inhaler "final" FDA approval letter under 35 U.S.C. § 156(d).

Specifically, and as attested to in the accompanying Declaration by Sjöholom, applicant notes that in *Unimed*, the Court found that "final FDA approval" triggering the 60 day time frame under 35 U.S.C. § 156(d) occurred once the FDA sent its final approval letter, and no further review or approval was required by the FDA, even though the DEA (Drug Enforcement Administration) had yet to give its final approval for marketing of the drug. Importantly, the Federal Circuit based its holding upon two important facts in that case that are clearly distinguished from the present case. To wit:

(1) The Court held that Section 156 creates a remedy ONLY for delay caused by governmental review by the FDA and not for other "governmental barriers" to full commercial and marketing permission

which may be caused by other governmental agencies, such as the DEA. Therefore, in the *Unimed* case, since only the DEA was causing the relevant "governmental bar" (and not the FDA), relief for the DEA imposed delay was not available under the 35 U.S.C. § 156;

(2) The Court also held that what is important under 35 U.S.C. § 156 is "the date of the FDA's letter ... giving final approval" for commercial marketing or use of the product -- any other governmental agency's requirements prior to marketing allowance are not important under the act. (see 12 U.S.P.Q.2d 1644, 1646 and 1647, emphasis added, case attached to Exhibit 3).

Hence, it can be seen from *Unimed* that the Federal Circuit has indicated that the final governmental approval that sets off the 60 day time frame under 35 U.S.C. § 156(d) is FINAL approval BY THE FDA to commercialize or use the product in the United States.

The facts in this case are squarely different from those considered by the Court in *Unimed*. Importantly, for example, in the present case, unlike *Unimed*, the delaying "governmental barrier" prior to which the nicotine inhaler could be unconditionally and finally, fully approved for marketing or use in the United States was entirely within the realm and power of the U.S. FDA, under statutes clearly contemplated to fall within 35 U.S.C. § 156(d). No other governmental agency's approval is at issue in this case.

Further, and as discussed above, the FDA's letter of May 2, 1997 clearly indicated that prior to "final" unconditional approval to market the nicotine inhaler, Pharmacia & Upjohn must satisfy the

FDA within 6-12 months that the product has been modified to become child-proof. As discussed above, and in the Declaration by Sjöholom, this necessary review and approval by the FDA before the inhaler could be unconditionally marketed, required the review and approval by the FDA of a supplemental NDA under Section 505(b) of the FFDCA.

Applicant submits that these facts plainly distinguish this case from that of *Unimed*. Indeed, from the Federal Circuit's teaching in *Unimed* that 35 U.S.C. § 156(d) depends upon the date that the FDA, as an agency, gives "final" unconditional approval to market or use a new drug indicates that in this case, the FDA's letter of May 2, 1997 was NOT the "final" unconditional, full approval letter which would initiate the running of the 60 day requirement for a drug extension application (as provided for under Section 156(d)).

Indeed, applicants submit that it was ONLY after the FDA, as an agency, completed review of the required supplemental New Drug Application covering the required child-resistant nicotine inhaler and "finally" approved its use in an unconditional manner that the requirements of Section 156(d) were met. Those requirements being met with the FDA's final and unconditional approval letter dated September 24, 1997 which finally and unconditionally approved a child-resistant Nicotrol® Inhaler for commercialization or use in the United States.

In summary, applicant submits that since the first "final," full, non-conditional FDA approval of the Nicotrol® Inhaler product

did not occur until September 24, 1997, when the FDA completed its review and mailed its final unconditional approval for marketing or using the nicotine inhaler, the sixty day time frame of 35 U.S.C. § 156(d)(1) runs until November 22, 1997 -- making the instant application timely filed.

(14) Prescribed fee.

The prescribed fee for receiving and acting upon the application for extension, $1,120.00 as prescribed in 37 C.F.R. § 1.20(j)(1), is attached hereto. Further, applicants hereby authorize the Commissioner to charge payment of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 16-2435.

(15) Name, address, and telephone number of the person to whom inquires and correspondence relating to the application for patent term extension are to be directed.

David L. Fox, Ph.D.
Reg. Number 40,612
PRAVEL, HEWITT, KIMBALL & KRIEGER
1177 West Loop South, Tenth Floor
Houston, Texas 77027-9095
Telephone: (504) 835-2000
Facsimile: (504)835-2070

(16) Duplicate, certified as such, of the application papers.

A duplicate of the application papers, certified as such, is

enclosed herewith.

Further, the undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. § 156,

including attachments and supporting papers, is being submitted as duplicate originals.

Dated: 21 November 1997

By: _____
David L. Fox, Reg. No. 40,612
Attorney for Pharmacia & Upjohn AB

PRAVEL, HEWITT, KIMBALL & KRIEGER
1177 West Loop South, Tenth Floor
Houston, Texas 77027-9095
Telephone: (504) 835-2000
Facsimile: (504)835-2070

(17) Declaration of attorney.

DECLARATION OF ATTORNEY

As provided for under 37 C.F.R. § 1.740(a)(17) and 1.740(b)(1)-(5), regarding the instant Request For Extension Of Patent Term Under 35 U.S.C. § 156 for U.S. Patent Number 5,167,242 and all accompanying papers, I aver that:

(a) I am a patent attorney authorized to practice before the Patent and Trademark Office and who has general authority from the owner of U.S. Patent Number 5,167,242, Pharmacia & Upjohn AB, to act on behalf of the owner in patent matters (Please see the Power Of Attorney attached hereto as Exhibit 1);

(b) I have reviewed and understand the contents of the instant application being submitted pursuant to this section;

(c) I believe, for the reasons argued and supported herein, that the patent is subject to extension pursuant to 37 C.F.R. § 1.710;

(d) I believe, for the reasons argued and supported herein, that an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations;

(e) I believe, for the reasons argued and supported herein, that the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720; and

(f) I further declare that all statements made herein of my

own knowledge are true; that all statements made on information and belief are believed to be true; that these statements are made with the knowledged that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any extension issuing therefrom.

Respectfully submitted,

Date: 21 November 1997

David L. Fox, Ph.D.
Registration Number 40,612
Attorney for Pharmacia & Upjohn AB

PRAVEL, HEWITT, KIMBALL & KRIEGER
1177 West Loop South, Tenth Floor
Houston, Texas 77027-9095
Telephone: (504) 835-2000
Facsimile: (504)835-2070

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail Number EM516876859US in an envelope addressed to: Assistant Commissioner for Patents, Box Patent Ext., Washington, D.C. 20231, on November 21, 1997.

David L. Fox, Ph.D.
Reg. Number 40,612

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,167,242

Patentee: Turner et al. Attn: Box Patent Extension

Issue date: December 1, 1992

Attorney Docket No.: A89675US

* * * * * * * * * * * * * * * *

POWER OF ATTORNEY AND DECLARATION BY PATENT OWNER,
PHARMACIA & UPJOHN AB,
RE. REQUEST FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. § 156

Honorable Commissioner of Patents
and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Applicant of the above-captioned Request For Extension Of Patent Term Under 35 U.S.C. § 156 for U.S. Patent Number 5,167,242, Pharmacia & Upjohn AB, a Corporation registered in Stockholm Sweden, hereby:

(a) States that it is the owner of record of the entire interest in and to U.S. Patent Number 5,167,242. Ownership is established by virtue of an assignment from the inventors to Pharmacia Aktiebolag, recorded July 31, 1990, in Reel 5388, Frames 0657-0674; as well as a name change document from Pharmacia AB to Pharmacia Aktiebolag recorded on October 28, 1991, at Reel 5941, Frames 0505-0515; and the following name change documents, filed herewith for recordation with the U.S. Patent and Trademark Office for Patent Number 5,167,242:

(i) A Swedish Certificate Of Registration (Registration No. 556029-7094) (one page) indicating that on 29th April, 1994 the Court gate its permission for the fusion of Kabi Pharmacia Aktiebolag ("AB") ("AB" is an abbreviation of Aktiebolag) to Pharmacia AB and thus the change in name of the owner of the 5,162,242 patent from Kabi Pharmacia Aktiebolag to Pharmacia AB became effective on April 29, 1994;

(ii) A Swedish Certificate Of Registration (Registration No. 556131-9608) (one page) indicating that on July 1, 1996 (1996-07-01) the owner of the 5,167,242 patent, Pharmacia AB, changed its name to its current name, Pharmacia & Upjohn AB;

(b) Appoints as its authorized attorneys the below listed registered patent attorneys, and authorizes them with power to execute and prosecute the instant Request For Extension Of Patent Term Under 35 U.S.C. § 156 for U.S. Patent Number 5,167,242 on behalf of Pharmacia & Upjohn AB as required under 37 C.F.R. § 1.730 and further authorizes them with general authority to act on behalf of Pharmacia & Upjohn AB in patent matters as required under 37 C.F.R. § 1.740(b):

David L. Fox, Reg. No. 40,612
Paul E. Krieger, Reg. No. 25,886
Jan K. Simpson, Reg. No. 33,283
Charles C. Garvey, Jr., Reg. No. 27,889
Greg C. Smith, Reg. No. 29,441

All of:
PRAVEL, HEWITT, KIMBALL & KRIEGER
1177 West Loop South, Tenth Floor
Houston, Texas 77027-9095
Telephone: (504) 835-2000;

(c) As the below identified official who is authorized to act on behalf of Pharmacia & Upjohn AB, I, John Hedenström, hereby additionally declare that:

(i) I have reviewed and understand the contents of the instant Request For Extension Of Patent Term Under 35 U.S.C. § 156 for U.S. Patent Number 5,167,242 and all related papers;

(ii) I believe, for the reasons argued and supported in the Request For Extension, that the patent is subject to extension pursuant to 37 C.F.R. § 1.710;

(iii) I believe, for the reasons argued and supported in the Request For Extension, that an extension of the length claimed in the Request For Extension is justified under 35 U.S.C. § 156 and the applicable regulations;

(iv) I believe, for the reasons argued and supported in the Request For Extension, that the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720; and

(v) I further declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful

false statements may jeopardize the validity of this application or any extension issuing therefrom.

Respectfully submitted,

Date: 21 Nov, 1997

John Hedenström
Patent Counsel
Pharmacia & Upjohn AB

DAC for Pats
111-1120 00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,167,242

Patentee: Turner et al. Attn: Box Patent Extension

Issue date: December 1, 1992

Attorney Docket No.: A89675US

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LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Honorable Commissioner of Patents
and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is an application for the extension of the term of U.S. Patent No. 5,167,242 and a duplicate of the papers thereof, certified as such.

A check in the amount of $1,120 to cover the filing fee is enclosed, as well as a post card for verification of receipt.

The following papers are being submitted herewith, in duplicate:

1. The present Transmittal letter with check and post card. (5 pages in total)

2. A complete application for extension of patent term (The Request For Extension Of Patent Term Under 35 U.S.C. § 156) complete in including at least, per 37 C.F.R. § 1.741:

(1) An identification of the approved product;

(2) An identification of each Federal statute under which

regulatory review occurred;

(3) An identification of the patent for which an extension is being sought;

(4) An identification of each claim of the patent which claims the approved product or a method of using or manufacturing the approved product;

(5) Sufficient information to enable the Commissioned to determine under 35 U.S.C. § 156 subsections (a) and (b) the eligibility of a patent for extension and the rights that will be derived from the extension and information to enable the Commissioned and the Secretary of Health and Human Services of the Secretary of Agriculture to determine the length of the regulatory review period; and

(6) A brief description of the activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

(43 pages in total)

3. EXHIBIT 1: Power Of Attorney and Declaration By Owner, including copies of two name change documents with recordation cover sheets and checks for the requisite fees, for recordation with the Patent Office.

(8 pages in total)

4. EXHIBIT 2: Draft FDA-Approved Product Insert For Nicotrol® Inhaler Product.

(16 pages in total)

5. EXHIBIT 3: Declaration by Anders Sjöholm, including a copy of three cases.

(24 pages in total)

6. EXHIBIT 4: Declaration by Sven-Börje, including a copy of a case and a dictionary page.

(13 pages in total)

7. EXHIBIT 5: Complete copy of U.S. Patent No. 5,167,242.

(7 pages in total)

8. EXHIBIT 6: Copy of PTO Receipt of 3.5 Year Maintenance Fee for U.S. Patent No. 5,167,242.

(2 pages in total)

9. EXHIBIT 7: FDA Letter Dated July 18, 1990 Regarding IND.

(2 pages in total)

10. EXHIBIT 8: FDA Letter Dated May 15, 1996 Regarding NDA.

(2 pages in total)

11. EXHIBIT 9: FDA Letter Dated May 2, 1997 Regarding NDA.

(3 pages in total)

12. EXHIBIT 10: FDA Letter Dated September 24, 1997 Regarding NDA.

(3 pages in total)

13. EXHIBIT 11: Declaration by Lars Nilsson.

(6 pages in total)

Total Number Of Pages Submitted (in duplicate) 134.

A duplicate of the application papers, certified as such, is

enclosed herewith. The undersigned hereby certifies that the attached application for extension of patent term under 35 U.S.C. § 156 for U.S. Patent Number 5,167,242, including attachments and supporting papers, is being submitted as duplicate originals.

Dated: 21 November 1997

By: _____
David L. Fox, Reg. No. 40,612
Attorney for Pharmacia & Upjohn AB

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 16-2435.

Respectfully submitted,

_____
David L. Fox, Ph.D.
Reg. Number 40,612

PRAVEL, HEWITT, KIMBALL & KRIEGER
1177 West Loop South, Tenth Floor
Houston, Texas 77027-9095
Telephone: (504) 835-2000

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail Number EM516876859US in an envelope addressed to: Assistant Commissioner for Patents, Box Patent Ext., Washington, D.C. 20231, on November 21, 1997.

David L. Fox, Ph.D.
Reg. Number 40,612

Exhibit 1

Exhibit 1 removed

2 checks

2 cover sheets

2 name changes

Pharmacia & Upjohn Aktie bolag

Pharmacia Aktie bolag

DRAFT

MAY 2 1997

2

NICOTROL® INHALER
(nicotine inhalation system) 10 mg/cartridge
(4 mg delivered)

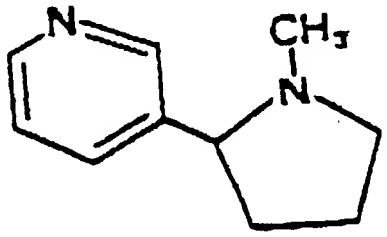
Description

NICOTROL® Inhaler (nicotine inhalation system) consists of a mouthpiece and a plastic cartridge delivering 4 mg of nicotine from a porous plug containing 10 mg nicotine. The cartridge is inserted into the mouthpiece prior to use.

Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, freely water-soluble, strongly alkaline, oily, volatile, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic pungent odor and turns brown on exposure to air or light. Of its two stereoisomers, S(-)nicotine is the more active. It is the prevalent form in tobacco, and is the form in the NICOTROL Inhaler. The free alkaloid is absorbed rapidly through the skin, mucous membranes, and respiratory tract.

Structural Formula:

[Picture]



Chemical Name: S-3-(1-methyl-2-pyrrolidinyl) pyridine

Molecular Formula: $C_{10}H_{14}N_2$

Molecular Weight: 162.23

Ionization Constants: $pKa_1 = 7.84$, $pKa_2 = 3.04$ at 15 C

Octanol-Water Partition Coefficient: 15:1 at pH 7

Nicotine is the active ingredient; inactive components of the product are menthol and a porous plug which are pharmacologically inactive.

Nicotine is released when air is inhaled through the Inhaler.

CLINICAL PHARMACOLOGY

Pharmacologic Action

Nicotine, the chief alkaloid in tobacco products, binds stereo-selectively to nicotinic-cholinergic receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions, and in the brain. Two types of central nervous system effects are believed to be the basis of nicotine's positively reinforcing properties. A stimulating effect is exerted mainly in the cortex via the locus ceruleus and a reward effect is exerted in the limbic system. At low doses the stimulant effects predominate while at high doses the reward effects predominate. Intermittent intravenous administration of nicotine activates neurohormonal pathways, releasing acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, beta-endorphin, growth hormone, and ACTH.

Pharmacodynamics

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia, and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than 1 hour), but not at the same rate for different physiologic effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms such as cigarette craving can be reduced in most individuals by plasma nicotine levels lower than those from smoking.

Withdrawal from nicotine in addicted individuals can be characterized by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue), and weight gain. Nicotine toxicity is characterized by nausea, abdominal pain, vomiting, diarrhea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respiration and hypotension.

Both smoking and nicotine can increase circulating cortisol and catecholamines, and tolerance does not develop to the catecholamine-releasing effects of nicotine. Changes in the response to a concomitantly administered adrenergic agonist or antagonist should be watched for when nicotine intake is altered during NICOTROL Inhaler therapy and/or smoking cessation (See PRECAUTIONS, Drug Interactions).

PHARMACOKINETICS

Absorption

Most of the nicotine released from the NICOTROL Inhaler is deposited in the mouth. Only a fraction of the dose released, less than 5%, reaches the lower respiratory tract. An intensive inhalation regimen (80 deep inhalations over 20 minutes) releases on the average 4 mg of the nicotine content of each cartridge of which about 2 mg is systemically absorbed. Peak plasma concentrations are typically reached within 15 minutes of the end of inhalation.

Absorption of nicotine through the buccal mucosa is relatively slow and the high and rapid rise followed by the decline in nicotine arterial plasma concentrations seen with cigarette smoking are not achieved with the inhaler. After use of the single inhaler the arterial nicotine concentrations rise slowly

to an average of 6 ng/mL in contrast to those of a cigarette, which increase rapidly and reach a mean C_{max} of approximately 49 ng/mL within 5 minutes.

The temperature dependency of nicotine release from the NICOTROL Inhaler was studied between 68°F and 104°F in eighteen patients. Average achievable steady state plasma levels after 20 minutes of an intensive inhalation regimen each hour at ambient room temperature are on the order of 23 ng/mL. The corresponding nicotine plasma levels achievable at 86°F and 104°F are on the order of 30 and 34 ng/mL.

Nicotine peak plasma concentration (C_{max}) at steady-state, after 20 minutes of an intensive inhalation regimen per hour, for 10 hours.

	C_{max} (ng/mL)		
	20°C/ 68°F	30°C/ 86°F	40°C/104°F
	N=18	N=18	N=18
Mean	22.5	29.7	34.0
S.D.	7.7	8.3	6.9
Min	11.1	17.6	24.1
Max	40.4	47.2	48.6

Ad libitum use of the NICOTROL Inhaler typically produces plasma levels of 6-8 ng/mL, corresponding to about 1/3 of those achieved with cigarette smoking.

Distribution

The volume of distribution following IV administration of nicotine is approximately 2 to 3 L/kg. Plasma protein binding of nicotine is <5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant effects on nicotine kinetics.

Metabolism

More than 20 metabolites of nicotine have been identified, all of which are less active than the parent compound. The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). Cotinine has a half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold. The major site for the metabolism of nicotine is the liver. The kidney and lung are also sites of nicotine metabolism.

Elimination

About 10% of the nicotine absorbed is excreted unchanged in the urine. This may be increased to up to 30% with high urine flow rates and urinary acidification below pH 5. The average plasma clearance is about 1.2 L/min in a healthy adult smoker. The apparent elimination half-life of nicotine is 1 to 2 hours.

Gender Differences

Intersubject variability coefficients of variation (C.V.) for the pharmacokinetic parameters (AUC and C_{max}) were approximately 40% and 30%, respectively, for males and females. There were no medically significant differences between females and males in the kinetics of NICOTROL Inhaler.

CLINICAL TRIALS

The efficacy of NICOTROL Inhaler therapy as an aid to smoking cessation was demonstrated in two single-center, placebo-controlled, double-blind trials with a total of 445 healthy patients. The number of Nicotrol Inhaler cartridges used was a minimum dose of 4 cartridges/day and a maximum dose of 20 cartridges/day.

In both studies, the recommended duration of treatment was 3 months; however, the patients were permitted to continue to use the product for up to 6 months, if they wished. The quit rates are the percentage of all persons initially enrolled who continuously abstained after week 2. NICOTROL Inhaler was more effective than placebo at 6 weeks, 3 months and 6 months. The efficacy is shown in the following table.

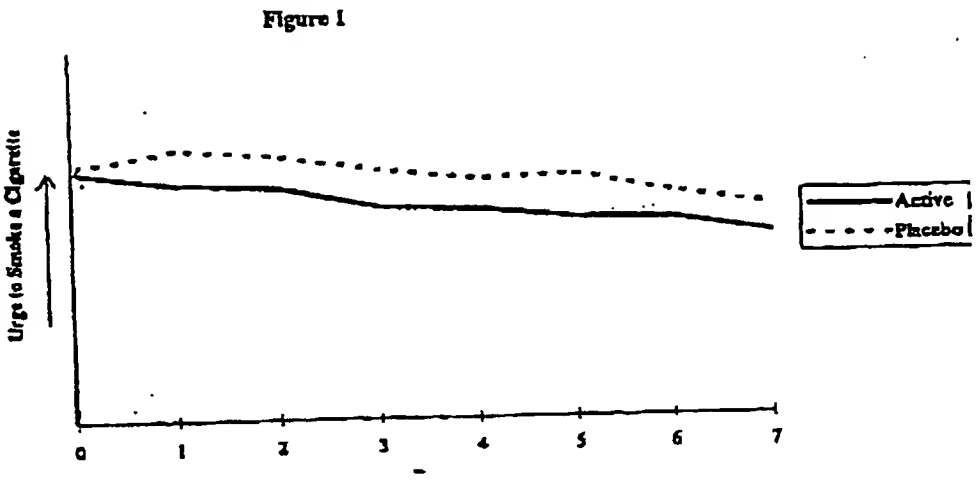
Quit Rates by Treatment
(N= 445 Patients in 2 Studies)

Group	Number of Patients	At 6 Weeks	At 3 Months	At 6 Months	At 12 Months*
Nicotrol Inhaler	223	44-45%	31-32%	20-21%	11-13%
Placebo	222	14-23%	8-15%	6-11%	5-10%

*Follow-up, patients not on treatment.

Patients who used NICOTROL Inhaler had a significant reduction in the "urge to smoke", a major nicotine withdrawal symptom, compared with placebo-treated patients throughout the first week, (see Figure).

Figure 1



INDICATIONS AND USAGE

NICOTROL Inhaler is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. NICOTROL Inhaler therapy is recommended for use as part of a comprehensive behavioral smoking cessation program.

CONTRAINDICATIONS

Use of NICOTROL Inhaler therapy is contraindicated in patients with known hypersensitivity or allergy to nicotine or to menthol.

WARNINGS

Nicotine from any source can be toxic and addictive. Smoking causes lung disease, cancer and heart disease, and may adversely affect pregnant women or the fetus. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy, Warning

Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. The Nicotrol Inhaler does not deliver hydrogen cyanide and carbon monoxide. However, nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that NICOTROL Inhaler can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by NICOTROL Inhaler has not been examined in pregnancy (See **PRECAUTIONS). Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.** If NICOTROL Inhaler is used during pregnancy, or if the patient becomes pregnant while using it, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children

This product contains nicotine and should be kept out of the reach of children and pets. The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if the nicotine from the Nicotrol Inhaler is inhaled, ingested or buccally absorbed by children or pets. A cartridge contains about 60% of its initial drug content when it is discarded, which is about 6 mg. Patients should be cautioned to keep both the used and unused cartridges of Nicotrol Inhaler out of the reach of children and pets.

All components of the NICOTROL Inhaler system should also be kept out of the reach of children and pets to avoid accidental swallowing and choking.

PRECAUTIONS

General

The patient should be urged to stop smoking completely when initiating NICOTROL Inhaler therapy (See DOSAGE AND ADMINISTRATION). Patients should be informed that if they continue to smoke while using the product, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the treatment should be discontinued (See WARNINGS). Physicians should anticipate that concomitant medications may need dosage adjustment (See Drug Interactions).

Sustained use (beyond 6 months) of NICOTROL Inhaler by patients who stop smoking has not been studied and is not recommended.(See DRUG ABUSE AND DEPENDENCE).

Bronchospastic Disease

Nicotrol Inhaler has not been specifically studied in asthma or chronic pulmonary disease. Nicotine is an airway irritant and might cause bronchospasm. Nicotrol Inhaler should be used with caution in patients with bronchospastic disease. Other forms of nicotine replacement might be preferable in patients with severe bronchospastic airway disease.

Cardiovascular or Peripheral Vascular Diseases

The risks of nicotine replacement in patients with cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina and Raynaud's phenomena) should be evaluated carefully before nicotine replacement is prescribed.

Tachycardia and palpitations have been reported occasionally with the use of NICOTROL Inhaler as well as with other nicotine replacement therapies. No serious cardiovascular events were reported in clinical studies with NICOTROL Inhaler, but if such symptoms occur, its use should be discontinued.

NICOTROL Inhaler generally should not be used in patients during the immediate post-myocardial infarction period, nor in patients with serious arrhythmias, or with severe or worsening angina.

Renal or Hepatic Insufficiency
The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (See **PHARMACOKINETICS**).

Endocrine Diseases
NICOTROL Inhaler therapy should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes, since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease
Nicotine delays healing in peptic ulcer disease; therefore, NICOTROL Inhaler therapy should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension
Nicotine therapy constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, NICOTROL Inhaler therapy should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for Patient
A patient information sheet is included in the package of NICOTROL Inhaler cartridges dispensed to the patient. Patients should be encouraged to read the information sheet carefully and to ask their physician and pharmacist about the proper use of the product (See **DOSAGE AND ADMINISTRATION**).

Patients must be advised to keep both used and unused cartridges out of the reach of children and pets.

Drug Interactions
Physiological changes resulting from smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications such as tricyclic antidepressants and theophylline. Doses of these and perhaps other medications may need to be adjusted in patients who successfully quit smoking.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidences of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine of rats.

Neither nicotine nor cotinine was mutagenic in the Ames salmonella test. Nicotine induced reparable DNA damage in an E. coli test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

PREGNANCY

Pregnancy Category D (See **WARNINGS** sections).

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of NICOTROL Inhaler therapy on fetal development are unknown. Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

NICOTROL Inhaler therapy should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of using it by the pregnant patient, who might continue to smoke.

Teratogenicity

Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when toxic doses were given to the dams (25 mg/kg IP or SC).

Human Studies: Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects

Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking one cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 μ g/kg/min nicotine to pregnant rhesus monkeys (equivalent to smoking about six cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low birth weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters have been studied near term. Cigarettes increased fetal aortic blood flow and heart rate and decreased uterine blood flow and fetal breathing movements. NICOTROL Inhaler has not been studied in pregnant women.

Labor and Delivery

NICOTROL Inhaler is not recommended for use during labor and delivery. The effect of nicotine on a mother or the fetus during labor is unknown.

Use in Nursing Mothers

Caution should be exercised when NICOTROL Inhaler is administered to nursing mothers. The safety of NICOTROL Inhaler therapy in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk to plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. Nicotine concentrations in milk can be expected to be lower with NICOTROL Inhaler when used as recommended than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from NICOTROL Inhaler therapy should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother (passive smoke exposure and contamination of breast milk with other components of tobacco smoke) and from NICOTROL Inhaler alone, or in combination with continued smoking.

Pediatric Use

Safety and effectiveness in pediatric and adolescent patients below the age of 18 years have not been established for any nicotine replacement product. However, no specific medical risk is known or expected in nicotine dependent adolescents. Nicotrol Inhaler should be used for the treatment of tobacco dependence in the older adolescent only if the potential benefit justifies the potential risk.

Geriatric Use

One hundred and thirty-two patients aged 60 or more participated in clinical trials of NICOTROL Inhaler. Nicotrol Inhaler appeared to be as effective in this age group as in younger smokers. Because medical conditions that are precautions to nicotine use are more common in the elderly, physicians should use care in prescribing this product to these patients.

ADVERSE REACTIONS

Assessment of adverse events in the 1,439 patients (730 on active drug), who participated in controlled clinical trials (including three dose finding studies) is complicated by the occurrence of signs and symptoms of nicotine withdrawal in some patients and nicotine excess in others. The incidence of adverse events is confounded by:1) the many minor complaints that smokers commonly have, 2) continued smoking by many patients, and 3) the local irritation from both the active drug and the placebo.

Local Irritation

NICOTROL Inhaler and the placebo were both associated with local irritant side effects. Local irritation in mouth and throat was reported by 40% of patients on active drug as compared to 18% of patients on placebo. Irritant effects were higher in the two pivotal trials with higher doses, being 66% on active drug and 42% on placebo. Coughing (32% active versus 12% placebo) and rhinitis (23% active versus 16% placebo) were also higher on active drug. The majority of patients rated these symptoms as mild.

The frequency of cough mouth and throat irritation declined with continued use of NICOTROL Inhaler. Other adverse events that occurred in over 3% of patients on active drug in placebo controlled pivotal trials considered possibly related to the local irritant effects of the inhaler are taste comments, pain in jaw and neck, tooth disorders and sinusitis.

Withdrawal
Symptoms of withdrawal were common in both active and placebo groups, Common withdrawal symptoms seen in over 3% of patients on active drug included: dizziness, anxiety, sleep disorder, depression, withdrawal syndrome, drug dependence, fatigue and myalgia.

Nicotine Related Adverse Events
The most common nicotine related adverse event was dyspepsia. This was present in 18% of patients in the active group compared to 9% of patients in the placebo group. Other nicotine related events present in greater than 3% of patients on active drug include nausea, diarrhea and hiccup.

Smoking Related Adverse Events
Smoking related adverse events present in greater than 3% of patients on active drug include chest discomfort, bronchitis and hypertension.

Other Adverse Events
Adverse events of unknown relationship to nicotine occurring in greater than 3% of patients on active drug include headache (26% on active drug and 15% on placebo), influenza-like symptoms, pain, back-pain, allergy, paraesthesias, flatulance and fever.

DRUG ABUSE AND DEPENDENCE

The NICOTROL Inhaler is likely to have a low abuse potential based on differences between the product and cigarettes in three characteristics commonly considered important in contributing to abuse; slower absorption, smaller fluctuations in blood levels and lower blood levels of nicotine. NICOTROL Inhaler, like many other nicotine-based smoking cessation therapies, does not produce arterial concentrations similar to cigarettes. However, nicotine withdrawal symptoms were noted in clinical trials at the time of Nicotrol Inhaler tapering and after Nicotrol Inhaler discontinuation.

Dependence might occur from transference of tobacco-related nicotine dependence to the NICOTROL Inhaler. The use of the inhaler beyond 6 months has not been evaluated in clinical trials and is not recommended. To minimize the risk of dependence, patients should be encouraged to withdraw gradually from NICOTROL Inhaler therapy after 3 months of usage (See DOSAGE AND ADMINISTRATION). If necessary, dose reduction can be achieved by gradual reduction of the dose over a 6 to 12 week period.

OVERDOSAGE

Signs and Symptoms of Nicotine Toxicity
Signs and symptoms of an overdose from the NICOTROL Inhaler would be expected to be the same as those of acute nicotine poisoning including: pallor, cold sweat, nausea, salivation, vomiting, abdominal pain, diarrhea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion, and weakness. Prostration, hypotension, and respiratory failure may ensue with large overdoses.

Lethal doses produce convulsions quickly and death follows as a result of peripheral or contral respiratory paralysis or, less frequently, cardiac failure.

Overdose from Inhalation

The oral LD_{50} for nicotine is >5 mg/kg in dogs and >24 mg/kg in rodents. Death is due to respiratory paralysis. The oral minimum acute lethal dose for nicotine in adult humans is reported to be 40 to 60 mg (<1 mg/kg). The effects of using several cartridges in rapid succession are unknown (See **WARNINGS, Safety Note Concerning Children**).

One cartridge of Nicotrol Inhaler contains 10 mg nicotine, of which approximately 4 mg is delivered nicotine. It is unlikely that an excessive nicotine overdose will occur via inhalation. Should such an overdose occur, however, with signs of nicotine poisoning, the patient should be instructed to contact his/her physician immediately. For additional emergency information, call your regional poison center or call the National Capital Poison Center toll free (1-800-498-8666).

Overdose from Ingestion

Persons ingesting NICOTROL Inhaler cartridges should be referred to a health care facility for management. In unconscious patients with a secure airway, instill activated charcoal via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal. Repeated doses of activated charcoal should be administered as long as the cartridge remains in the gastrointestinal tract since it will continue to release nicotine for many hours. The NICOTROL Inhaler cartridges can be identified with a radiogram.

Management of Nicotine Poisoning

Other supportive measures include diazepam or barbiturates for seizures, atropine for excessive bronchial secretions or diarrhea, respiratory support for respiratory failure, and vigorous fluid support for hypotension and cardiovascular collapse.

DOSAGE AND ADMINISTRATION

Patients must desire to stop smoking and should be instructed to ***stop smoking completely*** as they begin using NICOTROL Inhaler. It is important that patients understand the instructions, and have their questions answered. They should clearly understand the directions for using the NICOTROL Inhaler and safely disposing of the used cartridges.

The initial dosage of NICOTROL Inhaler is individualized. Patients may self-titrate to the level of nicotine they require. Most successful patients, in the clinical trials, used between 6 and 16 cartridges a day. Best effect was achieved by frequent continuous puffing (20 minutes). The recommended duration of treatment is 3 months, after which patients may be weaned from the NICOTROL Inhaler by gradual reduction of the daily dose over the following 6 to 12 weeks. The safety and efficacy of the continued use of NICOTROL Inhaler for periods longer than 6 months have not been studied and such use is not recommended.

Dosing recommendations are summarized in the table below.

RECOMMENDED DOSING

Duration		Recommended cartridges/day
INITIAL TREATMENT	12 Weeks	6 - 16
Gradual Reduction (if needed)	6-12 Weeks	No tapering strategy has been shown to be superior to any other in clinical studies.

Initial Treatment (Up to 12 Weeks)

For best results, patients should be encouraged to use at least 6 cartridges per day at least for the first 3 to 6 weeks of treatment. In clinical trials, the average daily dose was >6 (range 3 to18) cartridges for patients who successfully quit smoking. Additional doses may be needed to control the urge to smoke with a maximum of 16 cartridges daily for up to 12 weeks. Regular use of NICOTROL Inhaler during the first week of treatment may help patients adapt to the irritant effects of the product. Some patients may exhibit signs or symptoms of nicotine withdrawal or excess which will require an adjustment of the dosage (see Individualization of Dosage).

Gradual Reduction of Dose (Up to 12 weeks)

Most patients will need to gradually discontinue use of the NICOTROL Inhaler after the initial treatment period. Gradual reduction of dose may begin after twelve weeks of initial treatment and may last for up to twelve weeks. Recommended strategies for discontinuing use include suggesting to patients that they use the product less frequently, keep a tally of daily usage, try to meet a steadily reducing target or set a planned quit date for stopping use of the product.

Individualizing of Dosage

The Nicotrol Inhaler provides the smoker with adequate amounts of nicotine to reduce the urge to smoke, and may provide some degree of comfort by providing a hand-to-mouth ritual similar to smoking although the importance of such an effect in smoking cessation is, as yet, unknown.

The success of failure of smoking cessation is influenced by the quality, intensity and frequency of supportive care. Patients are more likely to quit smoking if they are seen frequently and participate in formal smoking cessation programs.

The goal of NICOTROL Inhaler therapy is complete abstinence. If a patient is unable to stop smoking by the fourth week of therapy, treatment should probably be discontinued.

Patients who fail to quit on any attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who were unsuccessful should be counseled and should then probably be given a therapeutic holiday before the next attempt. A new quit attempt should be encouraged when conditions are more favorable.

Based on the clinical trials, a reasonable approach to assisting patients in their attempt to quit smoking is to begin initial treatment, using the recommended dosage (See **DOSAGE AND ADMINISTRATION**). Dosage can then be adjusted in those patients with signs or symptoms of nicotine withdrawal or excess. Patients who are successfully abstinent on NICOTROL Inhaler should be treated at the selected dosage for up to 12 weeks, after which use of the Inhaler should be gradually reduced over the next 6 to 12 weeks. Some patients may not require gradual reduction of dosage and may abruptly stop treatment successfully. The safe use of this product for longer than six months has not been established.

The symptoms of nicotine withdrawal overlap those of nicotine excess (See **Pharmacodynamics and ADVERSE REACTION** sections). Since patients using NICOTROL Inhaler may also smoke intermittently, it is sometimes difficult to determine if they are experiencing nicotine withdrawal or nicotine excess. Controlled clinical trials of nicotine products suggest that palpitations, nausea and sweating are more often symptoms of nicotine excess, whereas anxiety, nervousness and irritability are more often symptoms of nicotine withdrawal.

SAFETY AND HANDLING

Disposal

See **patient information sheet** for information on handling and disposal. After using the NICOTROL Inhaler, carefully separate the mouthpiece, remove the used cartridge and throw it away, out of the reach of children and pets. Store the mouthpiece in the plastic storage case for further use. The mouthpiece is reusable and should be cleaned regularly with soap and water. The Nicotrol Inhaler cartridges can be detected on a radiogram.

How Supplied

NDC 0045-0000-00
NICOTROL INHALER (nicotine inhalation system) is supplied as 42 cartridges each containing 10 mg (4 mg is delivered) nicotine. Each unit consists of 1 mouthpiece, 7 storage trays each containing 6 cartridges and 1 plastic storage case.

A patient information leaflet is enclosed with the package. Store at room temperature not to exceed 30 °C (86°F). Protect cartridges from light.

CAUTION: Federal law prohibits dispensing without a prescription.

Manufactured by: Pharmacia & Upjohn AB, Sweden
Distributed by: McNEIL Consumer Products Co.
Division of McNEIL-PPC, Inc.
Fort Washington, PA 19034 USA
MADE IN SWEDEN

MAY 2 1997

Nicotrol® Inhaler

(nicotine inhalation system)
10 mg per cartridge
4 mg delivered

An Aid to Help You Stop Smoking

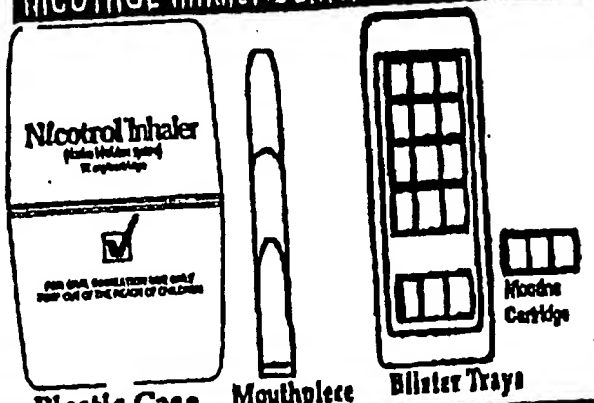
Patient Information

Read and follow carefully.
If you have questions or want more information, ask your doctor or pharmacist.

IMPORTANT INFORMATION - Read carefully

1. NICOTROL Inhaler helps you quit smoking by reducing your urge to smoke. Success in quitting with nicotine replacement therapy (such as NICOTROL Inhaler) usually involves behavior change.
   - Your doctor may adjust the number of Inhaler cartridges during the first few weeks. As your body adjusts to not smoking, your doctor will either tell you to stop using the Inhaler or slowly reduce the dose.
   - People who use Nicotrol Inhaler with a comprehensive behavioral smoking cessation program are more successful in quitting smoking. This program can include support groups, counselling or specific behavio change techniques as well as the Nicotrol Pathways to Change® self-help materials.
   - Call 1-800-699-5765 if you did not get your free Pathways to Change Starter Kit from your doctor.
2. Side Effects: Many people experience mild irritation of the mouth or throat, or cough when they first use the Nicotrol Inhaler. Most people get used to these effects in a short time.
3. Because you are already addicted to the nicotine in cigarettes, it is possible to stay dependent on the lower dose of nicotine found in the Nicotrol Inhaler. It is important to use the Inhaler for only as long as directed by your doctor to overcome your nicotine addiction and smoking habit.

NICOTROL Inhaler Contents



WARNINGS: Read before using NICOTROL Inhaler

1. Commit yourself - NO SMOKING! For the NICOTROL Inhaler to help, you must be firmly committed to quitting! Stop smoking as soon as you start using the Inhaler. Do not smoke or use any other tobacco products at any time while using the NICOTROL Inhaler.
   - Nicotine overdose can occur. If symptoms of overdose occur, call a doctor or Poison Control Center immediately. Overdose symptoms include: bad headaches, dizziness, upset stomach, drooling, vomiting, diarrhea, cold sweat, blurred vision, hearing difficulties, mental confusion, weakness and fainting.

2. Keep out of reach of children and pets.* The NICOTROL Inhaler can cause serious illness in children and pets - even in very small amounts. If a child chews on or swallows NICOTROL Inhaler cartridges, call a doctor or Poison Control Center. After a cartridge is used, throw away out of reach of children and pets. Even used cartridges contain enough nicotine to seriously harm children and pets.

3. Tell your doctor if you have:
   - heart problems (recent heart attack, irregular heartbeat, severe or worsening heart pain)
   - stomach ulcers
   - overactive thyroid
   - high blood pressure
   - allergies to drugs
   - diabetes requiring insulin
   - kidney or liver disease
   - wheezing or asthma
   - Tell your doctor about any medicines you are taking - the dosages may need to be changed. Check with your doctor before taking any new medicine while using NICOTROL Inhaler.
4. Do not use if you are pregnant (or think you may be pregnant) or nursing unless your doctor tells you to do so. Nicotine in any form can cause harm to your unborn baby. Only you and your doctor can decide if the benefits of using NICOTROL Inhaler to stop smoking outweigh the risks of using this medicine.

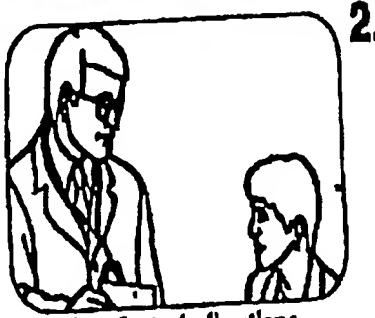
FOLLOW DIRECTIONS

Distributed by: McNeil Consumer Products Co.
Division of McNeil-PPC, Inc. 1997
Fort Washington, PA 19034 ©McN-PPC, Inc.
Made in Sweden
Manufactured for: Pharmacia & Upjohn AB, Sweden Rev 4/97

* The product is not child-resistant.

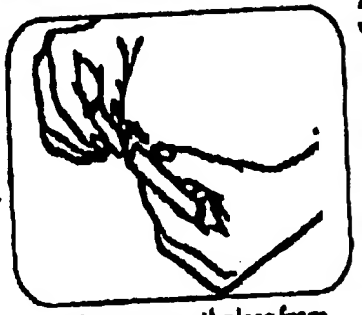
BEFORE YOU USE - Read information on both sides. FOLLOW ALL DIRECTIONS Exactly!

1.



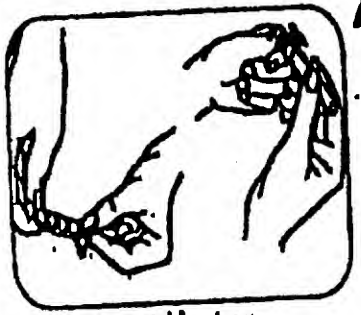
- Follow doctor's directions.
- Stop smoking completely during the NICOTROL Inhaler treatment program.

2.



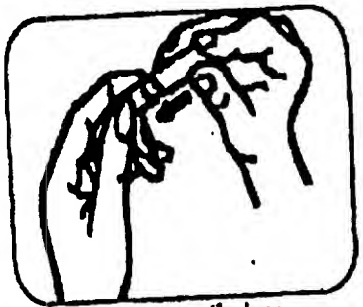
- Remove mouthpiece from plastic wrap.
- Pull off top.

3.



- Take out cartridge tray.
- Peel back to release 1 cartridge.
- Press cartridge firmly into bottom of mouthpiece until seal breaks.

4.



- Put top on mouthpiece.
- Press down firmly to break top seal of cartridge.
- Put cartridges back in plastic case when not in use.

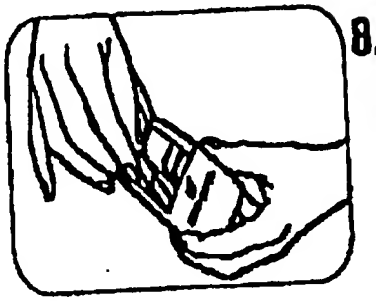
5.

- Inhale deeply into back of throat or puff in short breaths.
- As you inhale or puff through the mouthpiece, nicotine turns into a vapor and is absorbed into your mouth and throat.
- Use Inhaler longer and more often at first to help control cigarette cravings.
- Less nicotine per puff is released when you use Inhaler versus a cigarette.

6.

- Nicotine in cartridges is used up after about 20 minutes of active puffing.
- Try different schedules to help control cravings. Puffing on the Inhaler for 5 min. at a time will give you enough nicotine for 4 uses. In a few days you'll find what works best and know when nicotine in cartridges is used up.
- Use Inhaler at room temperature (above 60°F), cold temperatures reduce amount of nicotine you inhale.

7.



- When cartridge is empty, take off top of mouthpiece.
- Throw used cartridge away, out of reach of children and pets.
- When not in use always store mouthpiece and cartridges in plastic case, out of reach of children and pets.

8. READ & FOLLOW:

- Side Effects: You may experience mild irritation of the mouth or throat, or cough when you first use the Nicotrol Inhaler. You should get used to these effects in a short time.
- Do not use more than 16 cartridges each day, unless directed to do so by a physician.
- Do not use longer than 6 months.
- Store cartridges at room temperature, not to exceed 86°F.
- If you keep cartridges in car, be careful: interiors heat up quickly.
- Protect from light.
- Clean mouthpiece regularly with soap and water.

QUESTIONS? Call 1-800-699-5765

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,167,242

Patentee: Turner et al. Attn: Box Patent Extension

Issue date: December 1, 1992

Attorney Docket No.: A89675US

* * * * * * * * * * * * * * * * *

DECLARATION OF ANDERS SJÖHOLM REGARDING APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Honorable Commissioner of Patents
and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

I, Anders Sjöholm, a citizen of Sweden, do hereby declare that:

I am Category Director NRT (Nicotine Replacement Therapy) at Pharmacia & Upjohn Consumer Health Care, in Helsingborg, Sweden. I have been employed by Pharmacia & Upjohn (or its parent companies) from 1985-1988 and since 1995.

I have a formal education in social science and economics (with a BSc degree in social science and economics) and I have been working with the commercialization and marketing of nicotine and nicotine delivery products and technologies both internationally and in the United States while at Pharmacia & Upjohn. I am considered by my peers to be experienced and knowledgeable in the field relating to the commercialization and marketing of therapeutic nicotine delivery products, including such

commercialization and marketing within the United States.

I am familiar with the US FDA review and approval of Pharmacia & Upjohn's Nicotrol® Inhaler product, including the letter from the FDA dated September 24, 1997, signed by Albinnus D'Sa, Ph.D., and the letter from the FDA dated May 2, 1997, signed by Curtis Wright, M.D., M.P.H. (copies attached as Exhibits 9 and 10 of the accompanying Request For Extension Of Patent Term).

I have also read and am familiar with 35 U.S.C. § 156, including Section 156(d), and the following US court cases concerning 35 U.S.C. § 156(d): *Unimed, Inc. V. Quigg*, 12 U.S.P.Q.2d 1644 (Fed. Cir. 1989); *Mead Johnson Pharmaceutical Group v Bowen*, 6 USPQ2d 1565 (D.C.Cir. 1988); and *Norwich Eaton Pharmaceuticals, Inc. v. Bowen*, 808 F.2d 486 (6th Cir. 1987) (copies of these cases are attached).

In view of the above-noted FDA letters, statute, and cases, and in view of my experience with the regulation and commercialization of nicotine delivery products, I believe that, under 35 U.S.C. § 156(d), the "date the [Nicotrol® Inhaler] product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing and use" was September 24, 1997, the date the FDA mailed its final, non-conditional approval for the commercial marketing or use of Pharmacia & Upjohn's Nicotrol® Inhaler product.

I believe this because I believe that the letter from the FDA dated May 2, 1997 was NOT a final, nonconditional FDA permission for commercial marketing or use of the Nicotrol® Inhaler product.

Rather, I believe that the FDA letter of May 2, 1997 was only a conditional, non-final approval for marketing and use of the inhaler -- conditioned on Pharmacia & Upjohn modifying the product to sell only a modified child-resistant product within 6-12 months of the May 2, 1997 conditional approval. In effect, this represented a *de facto* bar to commercial marketing and use of a nonchild-resistant product.

I believe that the FDA's May 2, 1997 insistence upon a change to make the product child-resistant within 6-12 months represented a *de facto* bar to commercial marketing and use of the product because, from my experience in the art related to commercial products, including pharmacological commercial products, I understand that modification of a product to become child-resistant requires design and/or product changes. I am confident that, as a practical matter, no pharmaceutical company, or manufacturer of any commercial device, would undergo the time and expense of commercializing a first product only to have to replace that product with a redesigned and/or altered product in just 6 to 12 months.

This is borne out, in particular, by the facts in this case, of which I have personal knowledge. I believe that Pharmacia & Upjohn viewed the FDA's May 2, 1997 letter as a *de facto* bar to its commercialization and marketing in the U.S. for its Nicotrol® Inhaler product. I believe this because I know that Pharmacia & Upjohn made no attempt to market a nonchild-resistant version of its Nicotrol® Inhaler product following the May 2, 1997 letter

since they were told by the FDA that within 6-12 months of May 2, 1997 they would need to market an altered product, altered to be child-resistant. Indeed, rather than commercializing a nonchild-resistant Nicotrol® Inhaler product following the May 2, 1997 FDA letter, instead, Pharmacia & Upjohn redesigned the product and submitted the redesigned product to the FDA, in the form of a supplemental new drug application, filed with the FDA on July 15, 1997, for permission for actual, final and unconditional commercial marking and use in the U.S. for its Nicotrol® Inhaler product.

I am confident that Pharmacia & Upjohn followed this course of action and redesigned its inhaler product to be child resistant (filing a supplemental NDA seeking final nonconditional approval to market the child-resistant product), rather than attempting to produce, introduce, market and sell a nonchild resistant product for just 6-12 months because Pharmacia & Upjohn viewed the May 2, 1997 FDA letter as a *de facto* bar to commercializing any Nicotrol® Inhaler product until a child-resistant product was approved by the FDA for commercial marketing or use. In my opinion, there was simply no way that Pharmacia & Upjohn could have practically manufactured, introduced, marketed and sold a nonchild-resistant inhaler in the U.S. only to be required by the FDA to change the product to become child-resistant within a few months.

Further, I also believe that not only was the May 2, 1997 letter a practical, *de facto*, bar to Pharmacia & Upjohn marketing in the U.S. any Nicotrol® Inhaler product prior to development and approval of a child-resistant product, but the FDA letter dated May

2, 1997 can also be viewed as only a conditional, non-final approval of Pharmacia & Upjohn's Nicotrol® Inhaler product.

I believe this because I believe that it is clear from the FDA's letter of May 2nd (see page 2) that final approval for commercial marketing and use of the Nicotrol® Inhaler product is dependent/conditional upon Pharmacia & Upjohn modifying the inhaler to become child-resistant within 6-12 months. I believe that the effect of this wording in the FDA's letter of May 2, 1997 is to make final approval for marketing and use of the nicotine inhaler conditional and dependent upon the FDA reviewing and approving a child-resistant inhaler product within 6-12 months of the date of the letter.

I believe that Pharmacia & Upjohn regarded this to be the case, since, in fact, rather than marketing any inhaler product following the May 2, 1997 letter, they instead developed a child-resistant inhaler and submitted this product to the FDA for final, non-conditional approval for marketing or use of any inhaler in the United States.

Regarding the teachings of the three U.S. court cases cited above, and the comments made by applicant in the accompanying Request For Extension Of Patent Term, I agree that Pharmacia & Upjohn's position, as set forth in section 13(b) of the Request For Extension, is consistent with the statute and the cases. In particular, I agree that the May 2, 1997 FDA letter was not a final approval of the Nicotrol® Inhaler product, but, rather, acted as a *de facto* bar to commercial marketing or use of any inhaler until

Pharmacia & Upjohn could satisfy the FDA that it had a suitable child-resistant inhaler ready for marketing or use in the U.S. I further agree that any approval for marketing or use of the inhaler that may have been communicated in the May 2, 1997 letter was only conditional, non-final approval, contingent and dependent upon Pharmacia & Upjohn satisfying, within 6-12 months, the FDA that it had a suitable child-resistant inhaler ready for marketing or use in the U.S.

While I am not a lawyer, I agree that these positions are consistent with the three U.S. Court cases cited above as I understand them. Indeed, as I understand it, I agree that Pharmacia & Upjohn's position on these issues is actually strengthened and encouraged by the teachings of those cited cases. I believe that the "final" FDA approval for Pharmacia to commercially market or use its Nicotrol® Inhaler product in the U.S. was not communicated to Pharmacia & Upjohn until the final FDA approval letter dated September 24, 1997.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such

willful false statement may jeopardize the validity of the application or any extension issued thereon.

21 Nov 1997
Date

Anders Sjöholm

the claim itself. *See Corning Glass*, 868 F.2d at 1257 [9 USPQ2d at 1966] ("[w]e conclude that the claim preamble in this instance does not merely state a purpose or intended use for the claimed structure. Rather, those words do give 'life and meaning' and provide further positive limitations to the invention claimed.").

Accordingly, we find the appropriate field of prior art to be tablet-coating machines, of which the CIBA patent is the only cited reference. As stated by plaintiff's expert, who has been "involved with the design, manufacture and sale of tablet coating equipment and related devices for over fifteen years," the cited references other than CIBA "are used in a completely different art, more related to heavy industry." Affidavit of Gerald R. Zahradnik at ¶¶2 & 45. We also find that the needs of the pharmaceutical industry — specifically involving high standards of quality control, the fragile nature of the tablets and the like — differ significantly from those of heavy industry. *See* Zahradnik Affidavit at ¶7. Defendant has offered insufficient evidence to suggest that one of ordinary skill in the art would have looked to the separate field of heavy industrial machinery to find the solution to the tablet coating problem.

The CIBA patent for coating tablets discloses a perforated rib structure inside the drum, which is one of the designs the '347 patent distinguished as a "prior known apparatus [that has] serious disadvantages." Col. 1, line 29-30. The problems inherent in such a design, such as reduced interior volume of the drum and damage caused to the tablet coatings, col. 1, lines 48-52, col. 3, line 38, col. 4, line 21, are overcome by various features of the '347 patent, including the placement of the perforated areas and suction ducts about instead of within the drum. "When an attacker simply goes over the same ground travelled by the PTO, part of the burden is to show that the PTO was wrong in its decision to grant the patent." *American Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1360 [220 USPQ 763, 770-71] (Fed. Cir.), *cert. denied*, 469 U.S. 821 [224 USPQ 520] (1984). Defendant has failed to meet that burden. Accordingly, we find that CIBA and other prior art cited by the examiner do not render obvious the teachings of the '347 patent.

This finding is bolstered by the commercial success of plaintiff's product over prior tablet-coating machines, evidence that we consider relevant to our inquiry. See Zahradnik Affidavit at §§5-6 (describing success of patent licensee Vector Corporation's Hi-coater tablet-coating apparatus).

Lastly, we have considered and also reject defendant's argument, made during oral argument and in its papers, that the claim insufficiently defines the elements necessary to make a workable tablet-coating machine. Section 112 provides (emphasis added): "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter *which the applicant regards as his invention.*" 35 U.S.C. §112. The claim of the '347 patent even if it incompletely describes a workable machine, meets this requirement.

CONCLUSION

Defendant has failed to meet its burden of proving the invalidity of plaintiff's '347 patent by clear and convincing evidence. Discovery on the issue of patent infringement is to be completed by November 1, 1989. A Pre-Trial Order is to be submitted to the Court no later than November 15, 1989, and a Pre-Trial Conference will be held at 9:30 A.M. on November 22, 1989.

SO ORDERED.

Court of Appeals, Federal Circuit

Unimed Inc. v. Quigg

No. 89-1430

Decided October 23, 1989

PATENTS

1. Patent grant — Patent term extension; restoration (§105.17)

Patent Term Restoration Act's 60-day time limitation, 35 USC 156(d), within which application must be filed for extension of patent for human drug product, begins to run on date on which Food and Drug Administration approved drug for commercial marketing or use, and not on date on which Drug Enforcement Administration's rescheduling of drug was completed, even if DEA rescheduling is precondition to marketing of drug, since act takes into account only regulatory review carried out by FDA and does not contemplate any other governmental obstacles to marketing of drugs.

Appeal from the U.S. District Court for the District of Columbia, Revercomb, J.; 10 USPQ2d 1698.

Action by Unimed Inc. and Theodor Petrizilka against Donald J. Quigg, Commission-

er of Patents and Trademarks, seeking review of denial of patent term extension. From federal district court order setting aside commissioner's denial of application for extension, commissioner appeals. Reversed.

Harold D. Steinberg, of Steinberg & Raskin (Martin W. Schiffmiller, of Kirschstein, Ottinger, Israel & Schiffmiller, on brief), New York, N.Y., for plaintiffs-appellees.

Fred E. McKelvey, solicitor (Stuart E. Schiffer, acting assistant attorney general; Jay B. Stephens, U.S. attorney; Charles E. Van Horn, deputy solicitor, and Linda M. Skoro, assistant solicitor, on brief), for defendant-appellant.

Donald O. Beers, Stuart J. Land, Peter T. Grossi, Jr., William W. Vodra, and David E. Korn, of Arnold & Porter, Washington, D.C.; David A. Seligman and George W. Johnston, Nutley, N.J., for amicus curiae Hoffmann-La Roche Inc..

Before Skelton, senior circuit judge, and Archer and Mayer, circuit judges.

Mayer, J.

This is an appeal of the judgment of the United States District Court for the District of Columbia, 707 F.Supp. 17, 10 USPQ2d 1698 (1989), setting aside the Commissioner's denial of Theodor Petrzilka's application for extension of the term of U.S. Patent 3,668,224 pursuant to 35 U.S.C. §156 (Supp. II 1984) because the application was untimely. Unimed, Inc., is the exclusive licensee of the patent, and the appellees will be referred to jointly as "Unimed". The district court remanded the application to the Patent and Trademark Office for consideration on the merits and ordered it to grant an interim extension pending its final decision. We reverse.

Background

U.S. patent 3,668,224 describes and claims a process for making a dibenzo-pyran, which has the trade name Marinol. Marinol is the synthetic equivalent of an isomer of delta-9-tetrahydrocannabinol or THC, which is the principal psychoactive substance in *Cannabis sativa L.* marijuana. As exclusive licensee of the patent, Unimed submitted a New Drug Application (NDA) to the Food and Drug Administration on June 24, 1981 pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. §355, requesting approval of Marinol capsules for use as an antiemetic and antinauseant. By letter dated May 31, 1985, the FDA approved the NDA. The approval letter also stated, "We wish to remind you that MARINOL may not be legally marketed until the Drug Enforcement Administration has completed rescheduling activities as required by the Controlled Substances Act."

On May 13, 1986, the Drug Enforcement Administration finalized the removal of Marinol from Schedule I to Schedule II of the Controlled Substances Act, 21 U.S.C. §812, clearing the way for commercial marketing of the drug. Unimed's application for extension of the patent term pursuant to 35 U.S.C. §156 was filed in the PTO fourteen days after DEA rescheduled the drug, but more than a year after the FDA's final approval letter.

The PTO denied Unimed's application for extension of the patent term because it was not timely filed under 35 U.S.C. §156(d)(1). After an unsuccessful request for reconsideration, Unimed filed this suit, and the district court granted its motion for summary judgment.

Discussion

Title II of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, permits the term of a patent claiming a human drug product or method of using or manufacturing such a product to be extended for a period of time equal to the time the drug was subject to regulatory review. As a condition for extension of the patent term, the patent owner must submit an application to the Commissioner of Patents and Trademarks in accordance with section 156(d). 35 U.S.C. §156(a)(3). Section 156(d) provides:

> (1) . . . Such an application may only be submitted within the sixty-day period beginning on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use.

The "regulatory review period" for human drug products is defined in section 156(g)(1)(B):

> The regulatory review period for a human drug product is the sum of—
> (i) the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 became effective for the approved human drug product and ending on the date an application was initially submitted for

such drug product under section 351, 505, or 507, and

(ii) the period beginning on the date the application was initially submitted for the approved human drug product under section 351, subsection (b) of section 505, or section 507 and ending on the date such application was approved under such section.

Sections 505 and 507 are from the FFDCA, 21 U.S.C. §§355 and 357, and section 351 is from the Public Health Service Act, 42 U.S.C. §262. *See* 35 U.S.C. §156(f)(4).

The timeliness issue boils down to whether the sixty-day period specified in section 156(d)(1) began, as the Commissioner argues, when the FDA sent its approval letter, on May 31, 1985 or, as Unimed argues, when the DEA rescheduled Marinol nearly a year later. By Unimed's reckoning, because Marinol could not legally have been marketed until DEA rescheduling was complete, the sixty-day period under section 156(d)(1) did not begin until then. Unimed also tells us the FDA regarded DEA rescheduling as a precondition to marketing; indeed it goes a step further and argues that, from a practical standpoint, the FDA's approval of the NDA was contingent on DEA rescheduling.

We look first to the language of the statute. Unless it is ambiguous, the language Congress chose is conclusive of its meaning absent a clearly stated contrary intention. *Burlington N. R.R. v. Oklahoma Tax Comm'n*, 481 U.S. 454, 461, (1987).

[1] According to section 156(d)(1), the sixty-day period begins "on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use." Read in light of the definition of the "regulatory review period" in section 156(g)(1)(B), this language is crystal clear. In this case, "the provision of law under which the applicable regulatory review period occurred" is section 505 of the FFDCA, which governs the approval of new drugs by the FDA. There is no mention of DEA rescheduling or of 21 U.S.C. §811(a), the statute under which rescheduling takes place. Therefore, section 156(d)(1) admits of no other meaning than that the sixty-day period begins on the FDA approval date.

According to the FDA, the date of marketing approval for all new drugs is the date appearing on its approval letters. Two circuit courts of appeals have confirmed this, holding that, for purposes of the transitional provisions of Title I of the Drug Price Competition and Patent Term Restoration Act, 21 U.S.C. §355(j)(4)(D)(i) (Supp. II 1984), the date when a new drug is "approved" by the FDA is the date of the FDA approval letter, even where the applicant still needs to submit final printed labeling to the FDA. *Mead Johnson Pharmaceutical Group v. Bowen*, 838 F.2d 1332, 1337, 6 USPQ2d 1565, 1569 (D.C. Cir. 1988); *Norwich Eaton Pharmaceuticals, Inc. v. Bowen*, 808 F.2d 486, 491 (6th Cir. 1987).

Unimed thinks *Mead Johnson* and *Norwich Eaton* are different from this case because, as of the date of the FDA approval letters there, no "governmental" barrier to marketing the new drugs remained, whereas here, Unimed could not market the drug until the DEA had completed rescheduling. This distinction is impermissible because the Patent Term Restoration Act takes into account only the regulatory review carried out by the FDA and no other government obstacles to marketing new drugs. The May 31, 1985 letter to Unimed gave notice of the FDA's final approval to market Marinol; nothing more from the FDA was needed. DEA rescheduling was a legal prerequisite to Unimed's "commercial marketing or use" of Marinol, but "permission under the provision of law under which the applicable regulatory review period occurred" per section 156(d)(1) did not comprehend it.

Unimed's argument that the May 31, 1985 FDA letter was conditional is also unsound. The letter *reminded* Unimed that DEA rescheduling was necessary before the drug could be marketed. But this was not a condition on FDA approval, which declares only that the drug is safe and effective, not whether it should remain classified as a controlled substance. Acceptance of Unimed's view that, by the terms of the FDA approval letter, the new drug had not received "permission . . . for commercial marketing or use" would read important language out of the law. But we "must give effect, if possible, to every word of the statute." *Bowsher v. Merck & Co.*, 460 U.S. 824, 833 (1983).

Because subsections 156(d)(1) and 156(g)(1)(B) are clear and unambiguous, resort to the legislative history of the Patent Term Restoration Act is unnecessary to determine their meaning. Even if the history were contrary to the statutory language employed and passed, we would be bound by what the law says, not by what it "should" have said. Happily, the construction of these provisions which we confirm is nevertheless consistent with that record. Before the enactment of the present section 156, much broader coverage was rejected by the House of Representatives. The Senate bill would have allowed patent term extension for regulatory review under a variety of statutes besides the FFDCA and the Public Health

Service Act. *See* S. Rep. No. 138, 97th Cong. lst Sess. (1981). What became law was much more circumscribed and limited the extension only to the period of FDA review. *See* H.R. Rep. No. 857, 98th Cong., 2d Sess., Part II, 11 (1984), *reprinted in* 1984 U.S. Code Cong. & Admin. News 2686, 2695. For our purposes it does not matter why.

Contrary to Unimed, our resolution does not contravene the purpose of the Patent Term Restoration Act. The act was intended to ameliorate the loss incurred when patent terms tick away while the patented product is awaiting regulatory approval for marketing, but the scope of the relief was explicitly and precisely limited. And we can find no implication that the approval date that commences the running of the sixty-day application period under subsection (d) should be different from the approval date that marks the end of the regulatory review period under subsection (g)(1)(B)(ii).

Finally, this is purely a case of statutory interpretation, so the equitable considerations raised by Unimed are inappropriate. It may appear incongruous, at least in a case like this, that the operative review period would not include activities by other governmental entities that forestall marketing as effectively as FDA's, but it is not for us to distort the statute to "fix" what Congress either intentionally or inadvertently failed to anticipate. *TVA v. Hill*, 437 U.S. 153, 194 (1978). The sixty-day period specified in section 156(d)(1) commenced on May 31, 1985, the date of the FDA's letter to Unimed giving notice of its final approval of Marinol and Unimed's application for extension of the patent term was untimely.

Conclusion

Accordingly, the judgment of the district court is reversed.

REVERSED

District Court, N.D. Illinois

Whistler Corp. v. Dynascan Corp.

No. 88 C 8368

Decided July 17, 1989

PATENTS

1. Patentability/Validity — Anticipation — Prior public use or sale (§115.0706)

Patent infringement defendant which alleges that plaintiff's radar detector patent is invalid because it was in public use and on sale more than one year prior to filing of patent application, but which has failed to provide any direct testimony or evidence to show that detector was present at plaintiff's annual sales meeting held prior to critical date, has failed to establish prima facie case that detector was in public use prior to critical date.

Particular patents — Electrical — Radar detector

4,315,261, Mosher, radar signal detector, summary judgment of invalidity denied.

Patent infringement action brought by Whistler Corp. against Dynascan Corp. On defendant's motion for summary judgment of invalidity. Denied.

Paul J. Hayes, Victor B. Lebovici, and Eugene A. Feher, of Weingarten, Schurgin, Gagnebin & Hayes, Boston, Mass.; Robert B. Blasio, of McCullough, Campbell & Lane, Chicago, Ill., for plaintiff.

Russell E. Hattis and Robert E. Wagner, of Wallenstein, Wagner, Hattis, Strampel & Aubel, Chicago, for defendant.

Conlon, J.

Whistler Corporation ("Whistler") filed this patent infringement action against Dynascan Corporation ("Dynascan") alleging infringement of its radar signal detector U.S. Patent No. 4,315,261 ("the '261 patent"). Whistler moved for a preliminary injunction to enjoin Dynascan's manufacture and sale of four radar detectors. On February 9, 1989, this court denied Whistler's motion for a preliminary injunction. Dynascan now moves for summary judgment. For the reasons that follow, Dynascan's motion is denied.

DISCUSSION

A party is entitled to summary judgment when there is no genuine issue of material fact. Fed.R.Civ.P. 56(c). The party opposing the motion must make a showing sufficient to support the existence of a claimed factual dispute to require a judge or jury to resolve the conflicting versions of truth through a trial. *See Lemelson v. TRW, Inc.*, 760 F.2d 1254, 1260 [225 USPQ 697, 700-01] (Fed. Cir. 1985). Any doubt as to the presence or absence of any material fact must be resolved in favor the party opposing summary

ORDERED that the motion for preliminary injunction be denied.

II

[1] We vacate the order because the trial court failed to make sufficient findings of fact as mandated by Rule 52 of the Federal Rules of Civil Procedure. *Digital Equip. Corp. v. Emulex Corp.*, 805 F.2d 380, 382, 231 USPQ 779, 781 (Fed. Cir. 1986); *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 872-73, 228 USPQ 90, 97-98 (Fed. Cir. 1985). Rule 52(a) requires that the denial or grant of a preliminary injunction be supported by findings of fact. *Mayo v. Lakeland Highlands Canning Co.*, 309 U.S. 310, 316-17 (1940). "The rule does not place a severe burden upon the trial judge, for [she] 'need only make brief, definite, pertinent findings and conclusions upon the contested matters.'" *Loctite*, 781 F.2d at 872, 228 USPQ at 97 (quoting 5A J. Moore & J. Lucas, *Moore's Federal Practice* ¶52.06[1] at 52-138 (2d ed. 1985)). However, the trial court must provide sufficient factual findings such that we may meaningfully review the merits of its order. *Loctite*, 781 F.2d at 873, 228 USPQ at 98.

In denying the preliminary injunction, the trial court stated that it was "not convinced as to the probability of [Pretty Punch] prevailing on the merits when it comes to the issue of infringment [sic]" because there were "too many issues of fact yet to be determined." These statements represent the extent of the trial court's findings, and do not explain why Pretty Punch had not established a reasonable likelihood of success on the issue of infringement. Pretty Punch's expert testified in detail why Hauk's needle infringed the claims of the '445 patent; both sides briefed the infringement issue, yet the trial court provided this court with no guidance as to why and how it arrived at its conclusion. We have no basis for evaluating what facts entered into the trial court's infringement analysis, or if that analysis comports with the standards articulated by this court.

Furthermore, in analyzing irreparable injury the trial court improperly focused on Hauk's statement that she would be able to meet any damages due Pretty Punch. *See Atlas Powder Co. v. Ireco Chems.*, 773 F.2d 1230, 1233, 227 USPQ 289, 292 (Fed. Cir. 1985) (money award not sole remedy for future infringement). Thus the trial court erred in resolving whether or not irreparable harm had been established because it ignored other factual considerations raised by Pretty Punch.

We have indicated that "[w]here the trial court fails to make [sufficient] findings, the judgment will normally be vacated and the action remanded . . . ." *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1578, 221 USPQ 929, 933 (Fed. Cir. 1984); *see also Pullman-Standard v. Swint*, 456 U.S. 273, 291-92 (1982) (if trial court fails to make findings judgment should be vacated and remanded). This is such a case. "[W]e have nothing before us to which appropriate appellate standards of review can be applied with respect to the *merits* of the subject injunction." *Digital*, 805 F.2d at 383, 231 USPQ at 781 (emphasis in original). Thus, appellate review is impossible and the trial court's order must be vacated.

VACATED AND REMANDED

Court of Appeals, D.C. Circuit

Mead Johnson Pharmaceutical Group v. Bowen

No. 87-5099

Decided February 12, 1988

PATENTS

1. Patent term extension; restoration (§105.17)

Non-patent protection of products — In general (§130.01)

Food and Drug Administration's notification to company that its new drug application had been approved constitutes date of "approval" for determining whether drug is entitled to 10-year period of non-patent exclusivity under Drug Price Competition and Patent Term Restoration Act, which amended Federal Food, Drug, and Cosmetic Act, 21 USC 301 et seq., despite FDA's subsequent approvals of labeling supplements.

Appeal from U.S. District Court for the District of Columbia.

Mead Johnson Pharmaceutical Group and Mead Johnson & Co. sought preliminary and permanent injunctions as well as declaratory relief against U.S. Department of Health and Human Services (Food and Drug Administration). From federal district court decision granting defendant's motion for summary judgment, plaintiffs appeal. Affirmed.

Alan H Kaplan (Thomas O. Henteleff and Peter R. Mathers, on brief), Washington, D.C., for appellant.

Jacqueline H. Eagle and Kenneth L. Jost, Department of Justice (Richard K. Willard, assistant attorney general, Department of Justice, Joseph E. diGenova, U.S. attorney, Thomas Scarlett, David G. Adams, and Margaret A. Cotter, on brief), for appellees.

Before Edwards, Buckley, and Sentelle, circuit judges.

Edwards, J.

Mead Johnson Pharmaceutical Group ("Mead") appeals from a judgment of the District Court upholding the Food and Drug Administration's ("FDA") denial of a citizen petition filed by Mead. At issue is whether Mead is entitled to a ten-year period of nonpatent exclusivity for its drug "Desyrel" under the Drug Price Competition and Patent Term Restoration Act. The answer to that question turns solely on whether Mead's New Drug Application ("NDA") for Desyrel was "approved" by the FDA before or after January 1, 1982. There is little dispute about the facts; rather, the case centers on the meaning of the term "approved."

We find the FDA's construction of the statutory term "approved" to be consistent with congressional intent; and, even if the term "approved" might be viewed as ambiguous, it is clear that the FDA's construction was a permissible one. We therefore affirm the judgment of the District Court.

I. BACKGROUND

A. *Statutory Background*

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984), generally known as the "Hatch-Waxman Amendments" to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§301 *et seq.* The purpose of this legislation was to increase competition in the drug industry by facilitating the approval of generic copies of drugs. The Amendments notably eliminated the requirement that generic copies of drugs approved after 1962 be supported by independent clinical research data. Rather than complete the full — and very expensive — NDA process, generic copiers could proceed via an "Abbreviated New Drug Application" ("ANDA"), which required merely a reference to the safety and effectiveness data submitted by the "pioneer" drug manufacturer, along with submission of manufacturing and bioequivalence data for the generic copy. *See* 21 U.S.C. §355(j) (Supp. II 1984). The result was to make practical the manufacture of generic copies which theretofore had been uneconomical.

In order to compensate drug manufacturers who had invested in new drug development in reliance on the previous rules, as well as to provide continuing incentive for new drug research, the Amendments contained several provisions for varying periods of exclusivity before the FDA could approve ANDAs. One such provision is relevant to this case. As a transitional measure, the Amendments provided for a ten-year period of exclusivity for drugs "approved" by the FDA between January 1, 1982, and the enactment date of the Amendments, September 24, 1984. *See* 21 U.S.C. §355(j)(4)(D)(i) (Supp. II 1984). Drugs approved later had shorter periods of exclusivity, while those approved before January 1, 1982, enjoyed no exclusivity at all.

B. *The Desyrel NDA Approval*

Desyrel is Mead Johnson's trade name for Trazodone HCl, an antidepressant drug. Mead submitted a NDA for Desyrel in October 1978. On December 21, 1981, Dr. Marion Finkel of the FDA transmitted a letter to Mead informing it that review of the NDA was complete. This letter stated that approval would be forthcoming upon Mead's submission of revised printed labeling, in accordance with 4½ pages of detailed FDA comments. Letter from Marion J. Finkel to Mead Johnson and Company (Dec. 21, 1981), Joint Appendix ("J.A.") 150-54. Following several telephone conversations, Mead submitted, revised labeling the next day, incorporating the FDA's requested changes. In its accompanying letter, Mead stated its understanding, based on the telephone discussions, that "final approved labeling can be submitted subsequent to the approval of the NDA." Letter from Frank W. Furth to Marion Finkel (Dec. 22, 1981), J.A. 123. More telephone conversations apparently ensued, and on December 24 the FDA sent Mead a letter which stated in relevant part:

> We have completed our review of [the Desyrel] application as submitted with revised draft labeling on December 22, 1981 and have concluded the drug is safe and effective for use as recommended in the labeling. *Accordingly, the application is approved.*
>
> As agreed to over the phone this approval is granted with the understanding that any remaining issues regarding validation will be promptly and satisfactorily resolved and that final printed labeling will be promptly submitted and revised as follows before the drug is marketed.

Letter from Marion J. Finkel to Mead Johnson and Company (Dec. 24, 1981) (emphasis added), J.A. 9. There followed five specific requests for minor changes in language under the label's description of adverse reactions (such as changing "memory loss" to "impaired memory"). *Id.*[1]

In the December 1981 supplement to its "Approved Prescription Drug Products" list, the FDA listed Desyrel as approved. J.A. 81, 90. In the December 1981 "FDA Drug and Device Product Approvals" list, the FDA also listed Desyrel with an approval date of December 24, 1981. J.A. 94.

On January 19, 1982, Mead submitted the final printed labeling for Desyrel to the FDA with a cover letter that referenced "Your letter of approval for Desyrel . . . dated December 24, 1981." Letter from Robert F. Majewski to Marion Finkel (Jan. 19, 1982), J.A. 157. The FDA processed the final labeling as a "supplemental NDA." On February 1, 1982, in a letter to Mead signed by Dr. Paul Leber, a Division Director, the FDA stated: "We have completed our review and the supplement is approved." Letter from Paul Leber to Mead-Johnson Pharmaceutical Division (Feb. 1, 1982), J.A. 8.

After passage of the Hatch-Waxman Amendments, the FDA began to prepare for implementation by requesting drug manufacturers to submit information on their approved drugs. In response to such a request, Mead informed the FDA on October 22, 1984, that the approval date for Desyrel was December 24, 1981, and that it was not entitled to a period of statutory exclusivity. Letter from Marygayle Ritzert to Thomas J. McGinnis (Oct. 22, 1984), J.A. 129, 130. Six months later, however, on April 19, 1985 — just days before its patent on the drug was to expire — Mead wrote to the FDA to inform it that it had "reviewed our NDA file for DESYREL," that it had determined that the proper approval date was February 1, 1982, and that it was therefore entitled to an exclusivity period until February 1, 1992. Letter from Donald G. Harris to Peter H. Rheinstein (Apr. 19, 1985), J.A. 11-12.

C. *Proceedings Below*

On June 20, 1985, Mead filed a citizen petition with the FDA, requesting that it recognize a ten-year exclusivity period for Desyrel. Citizen Petition of Mead Johnson Pharmaceutical Group, J.A. 3-7. The FDA rejected the petition in a letter issued August 15, 1985. It found that Desyrel had been approved on December 24, 1981. It stated that the December 24 letter had approved the NDA, with the understanding that final labeling would be submitted before the drug was marketed, but that the letter had "neither stated not implied" that any further approval was necessary before the drug could be marketed. It added that agreement had been reached by telephone on the changes to be made, and that the ten-year exclusivity period depended only on the date of approval, not the date of marketing. The February 1 letter was clearly only an approval of a "labeling supplement" to a previously approved NDA; its author had had no authority to approve a NDA.[2] Letter from Harry M. Meyer to Alan H. Kaplan (Aug. 15, 1985), J.A. 13-15.

Mead submitted a Petition for Reconsideration on October 17, 1985, J.A. 20-43, which the FDA agreed to consider even though it was untimely. In its letter of December 12, 1985, denying the Petition for Reconsideration, Letter from Joseph P. Hile to Alan H. Kaplan (Dec. 12, 1985), J.A. 45-52, the FDA rejected Mead's argument that it had failed to consider provisions of the FDA's letter of December 21, 1981.[3] The agency maintained that the requirements contained in that letter had been modified by the ensuing telephone conversations between Mead and the FDA, as well as by the "approval" letter of December 24. J.A. 46-47. More generally, the FDA stated that, in

[1] In its denial of Mead's citizen petition, the FDA maintained that it and Mead had agreed by telephone on these five changes. Letter from Harry M. Meyer to Alan H. Kaplan (Aug. 15, 1985), J.A. 13, 14. The language of the December 24 letter ("As agreed to over the phone . . .") would seem to support this position. In a litigation affidavit not part of the administrative record, however, Mead's Dr. Frank Furth denies that there had been any such telephone agreement. Declaration of Frank W. Furth (Mar. 20, 1986), J.A. 169, 172.

[2] The FDA pointed out that Dr. Leber, the author of the February 1 letter, was a Division Director, and as such was authorized to approve a supplemental NDA, but not a NDA itself. Thus, it stated, if Mead was correct that the Desyrel NDA had not been approved on December 24, then it had never been approved at all. J.A. 14-15. Subsequently, Mead shifted its argument and maintained that "approval" had taken place when it submitted the final labeling on January 19.

[3] That letter had included the following statements: "Before the application may be approved, it will be necessary for you to submit revised printed labeling in accordance with our comments. . . ." J.A. 150. "If additional information relating to the safety or effectiveness of this drug becomes available before we receive final printed labeling, revision of that labeling may be required." J.A. 154.

accordance with 21 C.F.R. §314.105,[4] its policy had always been that "the date of the approval letter is the date of approval of the application." J.A. 49. In addition, the FDA emphasized that

> under the provisions of the agency's letter of December 24, 1981 the petitioner could have prepared final printed labeling, incorporating the appropriate changes, and marketed the product without additional agency action at anytime. Thus, contrary to petitioner's allegation Desyrel could have legally been marketed prior to January 19, 1982.

J.A. 50.

Finally, the FDA pointed out that at the time of the passage of the Hatch-Waxman Amendments, it had been a matter of public record (through information contained in FDA publications) that Desyrel had been approved on December 24, 1981. Thus, if Congress had intended Desyrel to enjoy the ten-year exclusivity provision, "it presumably would have selected a different cut-off date than it did." J.A. 51.

Several days after the FDA's denial of the Petition for Reconsideration, Mead filed a complaint in the District Court, seeking preliminary and permanent injunctions and declaratory relief. The District Court denied the request for a preliminary injunction, *Mead Johnson Pharmaceutical Group v. Bowen*, No. 85-3971 (D.D.C. Feb. 5, 1986), *reprinted in* J.A. 158-68, and subsequently granted the Government's motion for summary judgment, holding that the FDA's denial of Mead's citizen petition was not arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with law. *Mead Johnson Pharmaceutical Group v. Bowen*, No. 85-3971 (D.D.C. Jan. 27, 1987), *reprinted in* J.A. 213-25. Mead now appeals that decision.

II. ANALYSIS

This case presents "a pure question of statutory construction, [on which] our first job is to try to determine congressional intent, using 'traditional tools of statutory construction.' If we can do so, then that interpretation must be given effect. . . ." *NLRB v. United Food & Commercial Workers Union, Local 23*, 108 S.Ct. 413, 421 (1987) (quoting *INS v. Cardoza-Fonseca*, 107 S.Ct. 1207, 1221 (1987)). If, on the other hand, "the statute is silent or ambiguous with respect to the specific issue," *Chevron U.S.A. v. Natural Resources Defense Council*, 467 U.S. 837, 843 (1984), then the question for us becomes whether the FDA's construction of the statute is "permissible." *id.*, that is, one that is "rational and consistent with the statute." *United Food & Commercial Workers*, 108 S.Ct. at 421. In the present case, we find the FDA's interpretation of the statutory term "approved" in 21 U.S.C. §355 (j)(4)(D)(i) to be consistent with congressional intent; and, even if the term "approved" might be viewed as ambiguous, we have no doubt that the FDA's construction of it was a "permissible" one. *Chevron*, 467 U.S. at 843. Therefore, the agency's rejection of Mead's citizen petition cannot be held to be either "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. §706(2)(A) (1982).

[1] While the term "approved" is not defined in the statute, it had, at the time the Hatch-Waxman Amendments were enacted, a precise and undisputed meaning. By regulation the FDA had specified that "the applicant shall be notified in writing that the application is approved and *the application shall be approved on the date of the notification.*" 21 C.F.R. §314.105 (1981) (emphasis added).[5] As the District Court pointed out, the precise date of an "approval" was of great concern to the FDA, the NDA applicant, and competing drug manufacturers, even before the Hatch-Waxman Amendments. *Mead Johnson* (Jan. 27, 1987), slip op. at 10, J.A. 222. The FDA's regulation on this point thus reflected a well-considered, long-standing policy. We have found absolutely no reason to believe that Congress intended the term "approval" in the Hatch-Waxman Amendments to mean anything other than what the FDA understood it to mean.

It is undisputed that the FDA notified Mead that the Desyrel NDA was "approved" on December 24, 1981. Moreover, *both* the FDA and Mead considered approval to have taken place on that date. Indeed,

[4] 21 C.F.R. §314.105 (1981), as it existed in 1981-82, provided that when there was no longer any ground for denying approval, "the applicant shall be notified in writing that the application is approved and the application shall be approved on the date of the notification." The present version, 21 C.F.R. §314.105(a) (1987), provides: "The date of the agency's approval letter is the date of approval of the application."

[5] The FDA once considered approval to take place only upon satisfaction of any conditions contained in the notification of approval, *see* 21 C.F.R. §130.10 (1963), but in 1963 that policy was replaced by the current one. *See* 28 Fed. Reg. 6377, 6381 (1963). The pre-1963 definition is precisely the one Mead now urges on this court — twenty-five years too late.

Mead opens the "argument" section of its brief with this statement: "Mead Johnson does not dispute that, until enactment of the Hatch-Waxman Amendments, all parties including Mead Johnson were content to regard the DESYREL NDA as having been 'approved' as of December 24, 1981." Brief of Appellant at 14. Nor does Mead argue that, after December 24, any further action by the FDA was required before it could legally market the drug. Mead's counsel conceded at oral argument that, had Mead submitted the final labeling on December 26, it could then have marketed the drug without further agency action. And it is clear from Mead's letter of December 22, 1981, referring to the parties' understanding that "final approved labeling can be submitted subsequent to the approval of the NDA," [6] that neither Mead nor the FDA regarded the submission of such labeling as a precondition to "approval." [7]

We note finally that the Sixth Circuit last year decided a case virtually identical to this one. *Norwich Eaton Pharmaceuticals, Inc. v. Bowen*, 808 F.2d 486 (6th Cir. 1987). There, a drug manufacturer's NDA was approved on December 29, 1981, via a letter similar to the one at issue here,[8] but the final labeling was submitted to the FDA only in June 1985.[9] Nonetheless, the court had no difficulty in holding that the FDA's determination that the drug had been approved on December 29, 1981, was based on a permissible interpretation of the statute. We find ourselves in full agreement with the Sixth Circuit.

[6] Letter of Frank W. Furth to Marion Finkel (Dec. 22, 1981), J.A. 123.

[7] While the parties' subjective expectations are, of course, not dispositive of what Congress meant by the term "approved," they strengthen our conviction that there is no reason to believe Congress would have intended any definition other than that followed by the FDA. And Mead's December 22 letter certainly disposes of the argument that "it was well-established agency policy [in 1981] that final printed labeling had to be submitted and approved before an 'approval' letter would be sent." Brief of Appellant at 19.

[8] Mead attempts to distinguish the *Norwich* case on the ground that the FDA's letter there requested submission of the final labeling "when available." 808 F.2d at 492. Thus, Mead argues, Norwich's approval letter "did not contain any requirement that the final labeling be submitted to the agency prior to marketing the product." Brief of Appellant at 22. We fail to perceive any meaningful distinction in this context between the terms "when available" and "before the drug is marketed."

[9] The lengthy delay in that case was due to negotiations over the drug's status as a controlled substance.

CONCLUSION

We hold the FDA's interpretation of the term "approved" in 21 U.S.C. §355 (j)(4)(D)(i) to be consistent with congressional intent; and, even if the term "approved" might be viewed as ambiguous, it is clear that the FDA's construction was a permissible one. Accordingly, the judgment of the District Court is

Affirmed.

District Court, N. D. Illinois

Rockwell Graphic Systems Inc. v. Dev Industries Inc.

No. 84 C 6746

Decided June 4, 1987 and September 11, 1987

JUDICIAL PRACTICE AND PROCEDURE

1. Procedure — Contempt, sanctions (§410.49)

Defendants' failure to observe rules of discovery and to abide by court orders does not warrant entry of default judgment, in view of defendants' representation by series of attorneys, but does warrant imposition of sanctions against defendants.

Action by Rockwell Graphic Systems Inc., against Dev Industries Inc., Press Machinery Corp., Robert Fleck, and Pasquale Peloso, also known as Pat Peloso, for violations of 18 USC 1961-68. On plaintiff's renewed motion for default judgment, to hold defendants in contempt, and for other sanctions, and on defendants' motion for Rule 11 sanctions. Plaintiff's motion for sanctions granted.

Prior decision: 3 USPQ2d 1545.

Michael O. Warnecke, William P. Oberhardt, and Neuman Williams Anderson & Olson, all of Chicago, Ill., and Richard A. Speer, Pittsburgh, Pa., for plaintiff.

Stephen P. Carponelli, Gregory A. Adamski, James E. Hussey, and Carponelli Krug & Adamski, all of Chicago, Ill., for defendants.

McGarr, C.J.

The court has before it a renewed motion of Rockwell Graphic Systems for a default

adjudicate a personal claim or obligation unless it has jurisdiction over the person of the defendant." *Zenith Corp. v. Hazeltine*, 395 U.S. 100, 110, 89 S.Ct. 1562, 1569, 23 L.Ed.2d 129 (1969) (citations omitted). Finally, a long line of due process cases has held that adequate notice is required where individual interests may be adversely affected by a proceeding or adjudication. *See, e.g., Mullane v. Central Hanover Bank & Trust Co.*, 339 U.S. 306, 70 S.Ct. 652, 94 L.Ed. 865 (1950); *Green v. Lindsey*, 456 U.S. 444, 102 S.Ct. 1874, 72 L.Ed.2d 249 (1982).

For the foregoing reasons, the motion to "substitute" as granted by the District Court is constitutionally defective. Therefore, we find also that the judgment entered against the Estate cannot stand.

In view of our disposition of the case, we need not address other issues raised by the appellant. The judgment of the District Court is reversed.

NORWICH EATON PHARMACEUTICALS, INC., Plaintiff-Appellee,

v.

Otis R. BOWEN, Secretary of Health and Human Services; Frank E. Young, M.D., Ph.D., Commissioner of Food and Drugs; United States Food and Drug Administration, Defendants-Appellants.

No. 86-3397.

United States Court of Appeals, Sixth Circuit.

Argued Nov. 10, 1986.

Decided Jan. 9, 1987.

Pharmaceutical manufacturer brought action seeking declaration of its rights under Federal Food, Drug, and Cosmetic Act and injunction requiring recognition of nonpatent exclusivity period for marketing of drug. The United States District Court for the Southern District of Ohio, Carl B. Rubin, Chief Judge, 645 F.Supp. 321, granted injunction, and Government appealed. The Court of Appeals, Cornelia G. Kennedy, Circuit Judge, held that: (1) district court did not conduct improper trial de novo; (2) FDA approval of new drug application was effective even though it was issued prior to submission of final labeling; (3) approval of new drug application was effective as of date of approval by agency, and not date of notification of drug company; and (4) finding by FDA that approval of new drug application was effective as of date of approval and was thus not eligible for nonpatent marketing exclusivity was not arbitrary and capricious.

Reversed and remanded.

1. Administrative Law and Procedure ⇐746

Drugs and Narcotics ⇐10

District court did not conduct improper de novo review of decision of Food and Drug Administration, even though it did admit evidence not in administrative record, as additional evidence was required to determine whether administrative record was adequate, and district court decision was based on its review of administrative record, memoranda, and arguments of counsel. 5 U.S.C.A. § 706(2)(A).

2. Statutes ⇐219(6)

Position of Food and Drug Administration that it could approve new drug application prior to submission of final labeling was reasonable interpretation of statute where statute only required submission of proposed labeling and FDA regulation stated that approval would ordinarily follow submission of final labeling. Federal Food, Drug, and Cosmetic Act, § 505(b), (b)(1)(F), as amended, 21 U.S.C.A. § 355(b), (b)(1)(F); § 505(b)(6), 21 U.S.C.(1976 Ed.) § 355(b)(6).

3. Drugs and Narcotics ⇐10

Finding by Food and Drug Administration that approval of new drug application

was effective as of date of approval, not date of notification of drug company, was reasonable. Federal Food, Drug, and Cosmetic Act, § 505(c)(3)(D)(i), (j)(4)(D)(i), as amended, 21 U.S.C.A. § 355(c)(3)(D)(i), (j)(4)(D)(i).

4. Drugs and Narcotics ⇐9

Finding by Food and Drug Administration that new drug application approved on December 29, 1981, was effective as of date of approval, and that pharmaceutical manufacturer was thus not eligible for nonpatent exclusivity period for marketing of drug under terms of Drug Price Competition and Patent Term Restoration Act, was not arbitrary and capricious. 5 U.S.C.A. § 706(2)(A); Federal Food, Drug, and Cosmetic Act, §§ 505, 505(c)(3)(D)(ii), (j)(4)(D)(i, ii), as amended, 21 U.S.C.A. §§ 355, 355(c)(3)(D)(ii), (j)(4)(D)(i, ii).

Gerald F. Kaminski, Asst. U.S. Atty., Cincinnati, Ohio, Kenneth L. Jost, Dept. of Justice, Washington, D.C., Mark A. Heller, Assoc. Chief Counsel for Enforcement, Rockville, Md., Robert S. Greenspan, Richard A. Olderman argued, Appellate Staff, Dept. of Justice, Washington, D.C., for defendants-appellants.

Jonathan M. Norman, Cincinnati, Ohio, for amicus curiae Lymphomed, Inc.

Frank C. Woodside, III argued, Cincinnati, Ohio, Linda E. Roesch, Thomas O. Henteleff, Alan H. Kaplan, Peter R. Mathers, Washington, D.C., for plaintiff-appellee.

Before KENNEDY and NORRIS, Circuit Judges, and CONTIE, Senior Circuit Judge.

KENNEDY, Circuit Judge.

Defendants-appellants Otis R. Bowen, Secretary of Health and Human Services, *et al.* ("the Government") appeal from a judgment for plaintiff-appellee Norwich Eaton Pharmaceuticals, Inc. ("Norwich") in an action seeking a declaration of rights under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–392 ("FFDCA"). The Government argues that the District Court exceeded the appropriate scope of review and that the District Court erroneously found that the Food and Drug Administration's ("FDA") denial of Norwich's citizen petition was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. We find that the District Court reviewed the agency action under the appropriate standard, but we reverse its determination that the agency's action was invalid.

I.

Norwich is licensed by Reckitt and Colman, Ltd., an English pharmaceutical company, to distribute buprenorphine hydrochloride in the United States under the trade name Buprenex Injectible ("Buprenex"). Buprenex is a new analgesic drug used for treatment of moderate to severe pain. Because it is derived from the opiate thebaine, buprenorphine hydrochloride is a narcotic drug subject to control by the Drug Enforcement Administration ("DEA") under the Controlled Substances Act, 21 U.S.C. § 801 *et seq.* ("CSA"). As a derivative of thebaine, buprenorphine hydrochloride originally was automatically classified as a Schedule II substance under the CSA, which meant that it was subject to the most stringent controls applicable to a drug with legitimate medical use. Because of its unique molecular structure, however, buprenorphine hydrochloride does not have the physical dependence properties of the other opiates. This led to its reclassification in 1985 as a Schedule V drug, which is the lowest level of control short of decontrol.

On October 31, 1979, Norwich filed a New Drug Application ("NDA") with the FDA for Buprenex. At that time, buprenorphine hydrochloride had not been approved for marketing in the United States. On October 14, 1981, Dr. Marion Finkel of the FDA sent Norwich a letter stating that the NDA would be approved if Norwich made certain changes in the labeling. Dr. Finkel also stated that the drug was not marketable until the DEA had completed its final rulemaking procedures. At that

time, efforts were underway before the DEA to reclassify the drug from Schedule II to Schedule V of the CSA.

On December 29, 1981, Dr. Finkel sent a second letter to Norwich, in which she stated:

> We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the labeling. As discussed in a telephone conversation between Dr. Alexander Neill and Dr. Marion J. Finkel on December 22, 1981, you have agreed to the conditional Phase IV bioavailability study and the labeling revisions outlined in our October 14, 1981 letter. *Accordingly, the application is approved.*
>
> As you know, the Division is preparing documents to affect lesser controls for buprenorphine. *This, however, in no way impairs your approval to market buprenorphine in its current controlled substances schedule.*

Joint Appendix at 59 (emphasis added).

On January 27, 1982, Norwich submitted revised draft labeling to the FDA. On February 3, 1982, John M. Kolbas, the president of Norwich, sent a letter to the FDA acknowledging that the FDA had "approved" Buprenex and noting that the drug was currently subject to Schedule II controls. The letter stated further: "Although the letter approving the Buprenex NDA indicated that we may market the product under Schedule II controls, there are many factors which adversely affect the feasibility of this option." *Id.* at 383. Kolbas requested a meeting regarding the scheduling issue. On May 24, 1982, the FDA sent a letter to Norwich acknowledging receipt of Norwich's "supplemental application" providing for labeling changes and requesting additional changes in the label. Norwich submitted further labeling changes in September, 1984 and February and March, 1985. On February 28, 1985, the DEA ruled that buprenorphine hydrochloride was a Schedule V Narcotic Controlled Substance. On June 20, 1985, the FDA made its last request for changes in the labeling. On June 24, 1985, the FDA received final printed labeling from Norwich. On June 28, 1985, the labeling was approved. Norwich began marketing Buprenex on June 29, 1985.

Meanwhile, the Drug Price Competition and Patent Term Restoration Act, Pub.L. No. 98–417, 98 Stat. 1585 (amending 21 U.S.C. § 355) ("the Act"), became law on September 24, 1984. Title I of the Act is intended "to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962." H.R.Rep. No. 857, Part I, 98th Cong., 2d Sess. 14, *reprinted in* 1984 U.S.Code Cong. & Ad.News 2647, 2647. In addition, Title I provides a limited period of protection from competition to certain previously approved pioneer drugs by granting non-patent marketing exclusivity of ten years to new chemical entities approved on or after January 1, 1982 and on or before September 24, 1984, *see* 21 U.S.C. § 355(j)(4)(D)(i), (c)(3)(D)(i), and non-patent marketing exclusivity of five years to drugs approved after September 24, 1984, *see* 21 U.S.C. § 355(j)(4)(D)(ii), (c)(3)(D)(ii). Title II provides an incentive for pioneer drug research by "restor[ing] ... some of the time lost on patent life while the product is awaiting pre-market approval." H.R.Rep. No. 857, Part I, *supra*, at 15, *reprinted in* 1984 U.S.Code Cong. & Ad.News at 2648.

On August 19, 1985, Norwich filed a petition with the FDA seeking a declaration that Buprenex was entitled to exclusivity in marketing. Norwich argued that at the time of the 1981 "approval" there was no approved label under which the drug could have been marketed; thus, there was no valid approval. Norwich contended that approval actually came when the final printed label was submitted to the FDA in June, 1985. Norwich argued in the alternative that the approval became effective on January 8, 1982, which was the date on which Norwich received the FDA's letter of December 29, 1981. The FDA provided a detailed response denying this petition and stating that Buprenex had been approved

on December 29, 1981, before the statutory date allowing exclusivity.

Norwich brought suit in the United States District Court for the Southern District of Ohio. The District Court, 645 F.Supp. 321, held that Buprenex was not approved on December 29, 1981, but rather on June 28, 1985, the date on which the FDA approved an application for labeling that contained a Schedule V designation under the CSA. The Government appeals.

II.

The Government first raises a procedural issue; *i.e.*, that the District Court went beyond the administrative record in reviewing the agency's action. The District Court was required to review the agency's decision that Buprenex was approved in 1981 to determine whether that decision was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," as specified in 5 U.S.C. § 706(2)(A). The scope of review under this section is narrow: "In applying that standard, the focal point for judicial review should be the administrative record already in existence, not some new record made initially in the reviewing court." *Camp v. Pitts*, 411 U.S. 138, 142, 93 S.Ct. 1241, 1244, 36 L.Ed.2d 106 (1973). The Government asserts that the District Court erroneously conducted a trial *de novo* when it reviewed the FDA's action.

As this Court recently noted in *Upjohn Mfg. Co. v. Schweiker*, 681 F.2d 480 (6th Cir.1982), *de novo* review of agency action is the exception rather than the rule, unless required by statute. " '[*D*]*e novo* review is appropriate only where there are inadequate factfinding procedures in an adjudicatory proceeding, or where judicial proceedings are brought to enforce certain administrative actions.' " *Id.* at 483 (quoting *Camp v. Pitts*, 411 U.S. 138, 142, 93 S.Ct. 1241, 1244, 36 L.Ed.2d 106 (1973)).

The District Court did not conduct a trial *de novo* here. The District Court did admit evidence not in the administrative record. The Government objected, and the District Court responded that it could not determine whether the administrative record was adequate without seeing the documents that Norwich was offering. As the Ninth Circuit has recognized:

> It will often be impossible, especially when highly technical matters are involved, for the court to determine whether the agency took into consideration all relevant factors unless it looks outside the record to determine what matters the agency should have considered but did not.

Asarco, Inc. v. EPA, 616 F.2d 1153, 1160 (9th Cir.1980). Thus, consideration of evidence outside the administrative record is proper under some circumstances, *e.g.*, "for background information ... or for the limited purposes of ascertaining whether the agency considered all the relevant factors or fully explicated its course of conduct or grounds of decision." *Id.* (citations omitted).

[1] Moreover, the District Court stated in its Order that it based its decision upon its "review of the administrative record, the memoranda and the arguments by counsel." Joint Appendix at 263. The Order does not reveal that the District Court used any evidence outside the administrative record in reaching its decision. Thus, we find that the District Court did not conduct a trial *de novo* and that the Government's contention that the District Court based its decision on information outside the administrative record is without merit.

III.

On the merits, the Government appeals from the District Court's determination that Buprenex was not approved until June 28, 1985. We begin by noting that the proper issue for this Court to address, as it was for the District Court, is whether the FDA's determination on December 6, 1985 that Buprenex had been approved on December 29, 1981 was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.

The District Court found that the Secretary's decision that the December 29, 1981 letter constituted final approval of the Buprenex NDA was contrary to law because the FDA could not approve a drug before it received final printed labeling. Therefore, the Court concluded that the approval date was June 28, 1985, which is the date that the FDA approved the final printed labeling permitting sale of Buprenex as a Schedule V drug. Adoption of this date would give Norwich a 5–year exclusivity period. *See* 21 U.S.C. § 355(j)(4)(D)(ii), (c)(3)(D)(ii).

We cannot agree with the District Court's characterization of the law. We see nothing in either the statute or the regulations which would prohibit the FDA from approving a drug based upon proposed labeling as it purported to do in December, 1981.

The District Court began by noting that 21 U.S.C. § 355(b) requires the sponsor of a new drug to submit "specimens of the labeling proposed to be used for such drug" in its NDA before the application will be considered.[1] The Court also quoted 21 C.F.R. § 201.57(h)(1),[2] which requires that the schedule of a drug controlled by the DEA be stated in the labeling. The Court found that the DEA did not issue its final rule on the scheduling of buprenorphine hydrochloride until February 28, 1985, and that Norwich's label submissions before that date were thus insufficient to allow approval. The District Court also relied on 21 C.F.R. § 314.1(c)(4)(e) in finding that the FDA had a stated policy not to approve an NDA until the labeling was in its final form. This regulation, in its 1981 version, stated: "An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug." 21 C.F.R. § 314.1(c)(4)(e) (1981). The District Court thus concluded that the FDA's letter of December 29, 1981 merely indicated Buprenex's "approvable" status under 21 C.F.R. § 314.100(d)[3] and that "the FDA's 'approval' of the Buprenex NDA was contingent upon and not effective until approval of labeling in its final form." Joint Appendix at 264.

[2] We disagree. The FDA's interpretation that it was authorized in 1981 to approve a drug before final labeling was submitted does not conflict with the statute then in effect. Both the version of section 355(b) in effect in 1981, *see* 21 U.S.C. § 355(b)(6) (1976), and the amended version, *see* 21 U.S.C. § 355(b)(1)(F) (Supp. III 1985), require submission of "specimens of the labeling proposed to be used for such drug," but do not specifically require submission of the *final* labeling. Thus, the statute cannot be read to require submission of final printed labeling before approval. Nor do the regulations mandate this conclusion. The use of the word "ordinarily" in 21 C.F.R. § 314.1(c)(4)(e) (1981) logically implies that on some occasions the FDA will approve an application based on draft labeling. Moreover, the District Court's finding that the FDA's actions violated 21 C.F.R. § 201.57(h)(1) seems to ignore that buprenorphine hydrochloride *was* scheduled in December, 1981, although not under the classification desired by Norwich. Thus, the FDA approved Buprenex as a Schedule II drug in December, 1981, subject to Norwich's compliance with the agreed-upon changes in the draft label.[4]

1. This requirement was present in the version of the FFDCA in effect in 1981 and was not changed by the 1984 Act. *See* 21 U.S.C. § 355(b)(6) (1976); 21 U.S.C. § 355(b)(1)(F) (Supp. III 1985).

2. The language of this regulation remained the same from 1981 through 1986.

3. This regulation stated:

> On the basis of preliminary consideration of an application or supplemental application containing type-written or other draft labeling in lieu of final printed labeling, an applicant may be informed that such application is approvable when satisfactory final printed labeling identical in content to such draft copy is submitted.

21 C.F.R. § 314.100(d) (1981).

4. The FDA has since promulgated a regulation explicitly allowing approval based on draft labeling. See 21 C.F.R. § 314.105(b) (1986), which states:

> FDA will approve an application and issue the applicant an approval letter (rather than an approvable letter under § 314.110) on the basis of draft labeling if the only deficiencies

Because of its conclusion that approval did not come until June 28, 1985, the District Court did not address Norwich's alternative contention that the approval contained in the letter dated December 29, 1981 became effective on January 8, 1982, which is the date on which Norwich received the letter. If Norwich is correct, Buprenex is entitled to a 10–year exclusivity period. *See* 21 U.S.C. § 355(j)(4)(D)(i), (c)(3)(D)(i). We find that this interpretation is not mandated by the statute or the regulations.

The FDA regulation in effect at the time the letter was sent stated that "the application shall be approved on the date of the notification." 21 C.F.R. § 314.105 (1981). (The FDA has since amended the regulation to specifically provide that "[t]he date of the agency's approval letter is the date of approval of the application." 21 C.F.R. § 314.105(a) (1986).) The FDA interprets the 1981 regulation as meaning that approval was effective on the date on which it issued the approval letter, not the date on which the drug company received the letter. The FDA's interpretation is reasonable and enables it to fulfill its statutory mandate. Under 21 U.S.C. § 355(c), the FDA is required within 180 days of receiving an application for approval to either approve it or provide the applicant with notice of an opportunity for hearing on the question of whether the application is "approvable." Unless the FDA knows the date of notification, it cannot determine whether it fulfilled its statutory mandate.

"An agency's construction of a statute it is charged with enforcing is entitled to deference if it is reasonable and not in conflict with the expressed intent of Congress." *United States v. Riverside Bayview Homes, Inc.*, 474 U.S. 121, ___, 106 S.Ct. 455, 461, 88 L.Ed.2d 419 (1985) (citations omitted); *see also Aluminum Co. of America v. Central Lincoln Util. Dist.*, 467 U.S. 380, 389, 104 S.Ct. 2472, 2479, 81 L.Ed.2d 301 (1984). "[I]t is not necessary that the agency's construction of the statute be the only permissible one. Rather, its construction 'must be upheld unless that view is plainly *unreasonable.*' " *Ohio v. Ruckelshaus*, 776 F.2d 1333, 1339 (6th Cir. 1985) (quoting *National Steel Corp. v. Gorsuch*, 700 F.2d 314, 321 (6th Cir.1983)), *cert. denied*, — U.S. ——, 106 S.Ct. 2889, 90 L.Ed.2d 977 (1986).

[3] We find that the FDA's determination that it had issued a valid approval for Buprenex in 1981 was a reasonable interpretation under the FFDCA and the regulations promulgated thereunder and was not in conflict with expressed congressional intent. Thus, we see no grounds for holding that the FDA's determination was not in accordance with law.

IV.

The Government further contends that the FDA's determination that Buprenex's approval date was December 29, 1981 did not violate the prohibitions in 5 U.S.C. § 706(2)(A) against arbitrariness or capriciousness. We agree.

In its citizen petition, Norwich asserted that the regulatory history of Buprenex was "unique and potentially confusing in that, although an 'approval' letter was sent to Norwich Eaton on December 29, 1981, there did not exist at that time FDA approved labeling under which the product could have been marketed." Joint Appendix at 26. The company asked the FDA to declare that Buprenex was entitled to nonpatent marketing exclusivity, asserting that the effective approval date was June 28, 1985, or, in the alterntive, January 8, 1982. The FDA addressed each of the arguments raised by Norwich in its petition and concluded that the approval was effective on December 29, 1981.

The FDA began by rejecting Norwich's definition of "date of approval," as contained in the Act, as meaning either the

in the application concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

date on which a "meeting of the minds" occurred between the agency and the applicant as to the terms of the approval, or the date on which the applicant received the approval letter. The FDA also rejected Norwich's suggestion that an NDA could not be approved until the drug involved was cleared for marketing under the CSA. Rather, the FDA interpreted "date of approval" to mean "the date of [sic] which the agency exercises its authority under the Federal Food, Drug, and Cosmetic Act to approve a new drug application." Joint Appendix at 98.

The FDA pointed out that the language of its letter of December 29, 1981 clearly indicated that Buprenex was approved for marketing subject to Norwich making the agreed-upon changes in the label, and that FDA approval of the revised labeling was not a prerequisite to marketing. Under the provisions of the Act, the date of *approval,* not the date of marketing or distribution, determines whether exclusivity is available.

Kolbas' letter of February 3, 1982 to the FDA acknowledged that Buprenex was approved. Although the FDA admitted that it recommended additional changes to the labeling submitted by Norwich on January 27, 1982, it found these recommendations to be "irrelevant" to the date of approval. Norwich could have prepared final printed labeling in accordance with the December 29, 1981 letter and could have marketed Buprenex without further agency action. The 1981 letter requested submission only of final printed labeling and a market package of the drug when available. Moreover, Dr. Finkel, of the FDA, had told Norwich on December 22, 1981 that draft labeling need not be submitted. Instead of preparing final labeling and marketing the drug, however, Norwich choose to submit a supplement containing draft labeling. The FDA assigned these submissions an "S" file number, indicating that it regarded them as supplements, not amendments, to the original NDA. ("Amendments" are used to modify pending applications. *See* 21 C.F.R. § 314.6 (1981 through 1984 eds.). "Supplements" effect changes in applications that have already been approved. *See* 21 C.F.R. § 314.8 (1981 through 1984 eds.).) Although the FDA commented on and suggested changes to this draft labeling, these submissions in no way prevented Norwich from going ahead and marketing Buprenex in accordance with the provisions of the 1981 letter.

The FDA asserted that its June 28, 1985 letter merely approved an amendment to the 1982 labeling supplement to the previously approved NDA. It pointed out that the 1985 letter was signed by a division director, who was authorized solely to approve supplemental, not new, drug applications. Thus, if the FDA were to accept Norwich's assertion that the 1981 approval was not effective, the 1985 "approval" still would not be effective since it would not have been approved by someone with proper authority.

The FDA then stated that Norwich was incorrect in thinking that ability to market a drug under the CSA was a condition precedent to approval under the FFDCA. The agency admitted that its letter of October 14, 1981 to Norwich erroneously indicated that final rulemaking under the CSA would be necessary before legal marketing could occur. As the December 29, 1981 letter stated, however, buprenorphine hydrochloride was scheduled at the time of the 1981 approval. Thus, Norwich could have marketed the drug at the time of the 1981 approval as a Schedule II drug. Its decision not to do so was a marketing decision, not a result compelled by law.

The FDA acknowledged that a FDA employee had refused to certify Buprenex as being approved for marketing in the United States in December, 1984, pending the agency's receipt of the address of the manufacturing facility and copies of the final printed labeling. However, the agency asserted that this refusal reflected agency policy not to provide certification without this information. It did not indicate that the FDA did not consider the drug approved.

The FDA also noted that a copy of a May 12, 1982 recommendation of the Depart-

ment of Health and Human Services to the DEA that buprenorphine hydrochloride be rescheduled was provided to Norwich's counsel. This recommendation clearly stated that the drug was approved, thus providing Norwich's counsel with notice of the agency's interpretation of the 1981 letter.

Finally, the agency admitted that Buprenex was initially included in the fifth edition of the agency's Approved Prescription Drug Products publication, but was omitted in later supplements. The FDA explained that Buprenex was dropped from the list because agency policy at the time was to list only those approved drugs being marketed. The agency stated that since it now appeared that Buprenex would be marketed, the drug would again appear in the publication.

In reviewing for a violation of 5 U.S.C. § 706(2)(A), "the court must consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 416, 91 S.Ct. 814, 823, 28 L.Ed.2d 136 (1971) (citations omitted). The reviewing "court may not concern itself with the wisdom of agency action." *Federal Property Mgt. Corp. v. Harris*, 603 F.2d 1226, 1230 (6th Cir.1979) (citing *United States v. Allegheny-Ludlum Steel Corp.*, 406 U.S. 742, 749, 92 S.Ct. 1941, 1946, 32 L.Ed.2d 453 (1972)). "The court is not empowered to substitute its judgment for that of the agency." *Overton Park*, 401 U.S. at 416, 91 S.Ct. at 824. Rather, "[i]f the reasoning behind the agency's action is logical, ... that action must be allowed to stand. That is true even if an alternative course of action would also be logical ...." *Harris*, 603 F.2d at 1231.

[4] The FDA's denial of Norwich's citizen petition fully considered the arguments raised in the petition and rested upon a rational basis supported by the administrative record. Therefore, we find that the agency's determination in 1985 that Buprenex was approved in 1981 does not violate 5 U.S.C. § 706(2)(A).

V.

Accordingly, we REVERSE the District Court. The case is REMANDED to the District Court with directions to enter judgment for the Government.

Curtis L. WRENN, Plaintiff-Appellant, Cross-Appellee,

v.

Sylvester M. GOULD, Jr., Individually and as President, Cordelia Martin Health Center; Neighborhood Health Association of Toledo, Inc., d/b/a Cordelia Martin Health Center, Defendants-Appellees, Cross-Appellants.

Nos. 85–3285, 85–3315.

United States Court of Appeals, Sixth Circuit.

Submitted Aug. 5, 1986.

Decided Jan. 9, 1987.

Unsuccessful job applicant sought damages from not-for-profit employer providing health care to the indigent, claiming that he had been rejected from position in retaliation for having filed earlier civil rights claim against previous employer. The United States District Court for the Northern District of Ohio, John W. Potter, J., dismissed Title VI claim against employer, Title VI and Title VII claims against employer's president individually, and entered judgment in favor of employer on Title VII retaliation claim. Plaintiff appealed and employer cross-appealed. The Court of Appeals, Ryan, Circuit Judge, held that: (1) job applicant established prima facie case of retaliatory nonhiring, and (2) employer's reasons for hiring first job applicant, rather than job applicant involved

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,167,242

Patentee: Turner et al. Attn: Box Patent Extension

Issue date: December 1, 1992

Attorney Docket NO.: A89675US

* * * * * * * * * * * * * * * * *

DECLARATION OF SVEN-BÖRJE ANDERSSON REGARDING APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Honorable Commissioner of Patents
and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

I, Sven-Börje Andersson, a citizen of Sweden, do hereby declare that:

I am an employee (chemist) at Pharmacia & Upjohn Consumer Health Care, in Helsingborg, Sweden. I have been employed by Pharmacia & Upjohn (or its parent companies) since 1972.

I have a formal education in chemistry (with a BSc degree in natural sciences) and I have been working with nicotine and nicotine delivery products and technologies since 1987. I am considered by my peers to be experienced and knowledgeable in the art relating to nicotine and the therapeutic delivery of nicotine, such as by using nicotine delivery products.

I am familiar with the US FDA approval of the nicotine delivery products Nicorette® (chewing gum), Nicotrol® - nicotine transdermal system, Nicotrol® - nicotine nasal spray, and the

subject of the present request for patent term extension, the Nicotrol® Inhaler.

I understand that patent term extension is only available under 35 U.S.C. § 156 following the first FDA approval of the active ingredient of a drug product.

I believe that the recent FDA approval of the Nicotrol® Inhaler represents the first FDA approval of the active ingredient of the product, VAPOR PHASE NICOTINE.

The active ingredient delivered from the Nicotrol® Inhaler is VAPOR PHASE NICOTINE

I believe that the active ingredient delivered from the Nicotrol® Inhaler upon administration of the drug product is the evaporable "free-base nicotine" which is delivered as VAPOR PHASE NICOTINE (i.e., nicotine in its gaseous form). I understand that under *Glaxco Operations UK Ltd. v. Quigg*, 13 USPQ2d 1628 (Fed. Cir. 1990) (copy attached hereto) the term "active ingredient" in 35 U.S.C. § 156 means the active ingredient of the drug when administered.

The delivered active ingredient of the Nicotrol® Inhaler is VAPOR PHASE NICOTINE. This is because in administration of the active ingredient to the patent, it is solely GASEOUS NICOTINE that is inhaled from the inhaler by the patient. While the pre-used inhaler contains nicotine associated with a porous plug, as indicated on page 1 of the FDA-approved Nicotrol® Inhaler Draft Product Insert (see Exhibit 2 to the extension request), when the product is administered, the active ingredient "[n]icotine is

released when air is inhaled through the Inhaler." It is only VAPOR PHASE NICOTINE that is administered from the product to the patient (i.e., the nicotine associated with the plug must first be volatilized in order to be sucked as a vapor from the device by the patient and administered to the patient as a vapor by inhalation). Hence, it is clear that the active ingredient of the Nicotrol® Inhaler when the product is administered is VAPOR PHASE NICOTINE.

Prior FDA approvals related to nicotine delivery products did not approve the present active ingredient, NICOTINE VAPOR

I am aware of earlier FDA approvals of other active ingredients associated with nicotine delivery products, but none which concern the delivery of NICOTINE VAPOR as the active ingredient.

Specifically, I understand that on January 13, 1984, Merrell Dow received FDA approval for Nicorette® nicotine-containing chewing gum. However, the active ingredient of this product was not NICOTINE VAPOR. Rather, I understand that the registered drug substance was "nicotine polacrilex." I understand that nicotine was present in an ion-exchange complex; the nicotine was only released when the gum was actively chewed (i.e., if the gum just resided in the mouth, no nicotine would be administered); and that administration was to the mucosa in the mouth.

I am familiar with Pharmacia & Upjohn's FDA approval of its Nicotrol® - nicotine transdermal system which occurred on April 22, 1992. In that product, the nicotine was present, and administered to the patient in a liquid state via transdermal administration,

the delivery being controlled through diffusion in the adhesive of the patch.

I am also familiar with Pharmacia & Upjohn's FDA approval of its Nicotrol® - nicotine nasal spray. On March 22, 1996 the FDA approved this product having as its active ingredient diluted liquid phase nicotine, being administered in droplet (microdroplet) form to the nasal mucosa.

Unlike the other FDA approvals of any other nicotine-related products that applicant is aware of, the vapor phase product is unique in at least the way that it administers its unique active ingredient at the time of administration since, in at least some extent it mimics actual cigarette smoking, taking into account the behavioral nature of smoking (hand movement to the lips and inhalation or puffing), but distinct from the inhalation of harmful cigarette smoke into the lungs.

In further support of my assertion that the FDA-approved active ingredient of the Nicotrol® Inhaler, VAPOR PHASE NICOTINE, is a separate active ingredient from anything previously approved by the FDA, I note that the Concise® Oxford Dictionary defines "VAPOR" as a unique medicinal agent for inhaling ("Vapor:...a **medicinal agent for inhaling**" see attachment hereto). I believe that this commonly accepted definition of "VAPOR," as a distinct medicinal agent, further, and clearly, distinguishes -- AS A DIFFERENT AND DISTINCT ACTIVE INGREDIENT -- the use (administration) of a VAPOR as the active ingredient from, for example, the use (administration) of any other form(s) of a

compound.

In sumary, I believe it is quite reasonable to say that the "active ingredient" (especially as defined by the *Glaxco Operations UK Ltd.* case as being the ingredient of the drug which is active when the drug is administered) is VAPOR PHASE NICOTINE.

I believe that the "active ingredient" of the Nicotrol® Inhaler, VAPOR PHASE NICOTINE, is a different active ingredient from that of any other forms of nicotine that have previously been approved by the FDA. The "active ingredient" of the inhaler is simply not the same as those already approved by the FDA.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any extension issued thereon.

21 Nov, 1997
Date

Sven-Börje Andersson
Sven-Börje Andersson

nilsson.dec/sng

balance, the factors, when weighed accordingly, are in favor of plaintiff. We are accordingly persuaded that customers familiar with plaintiff's personal care products bearing the SUAVE mark would, upon encountering defendant's SUAVE marks for shoes, be likely to believe that the respective goods were manufactured by the same entity or that they were associated with or sponsored by the same producer.

[7] Decision: The opposition is sustained and registration to applicant is refused. The petition for cancellation is granted and Registration No. 1,169,440 will be cancelled in due course.

Court of Appeals, Federal Circuit

Glaxo Operations UK Ltd. v. Quigg

No. 89-1407

Decided January 24, 1990

PATENTS

1. Practice and procedure in U.S. Patent and Trademark Office — Commissioner — In general (§110.1901)

JUDICIAL PRACTICE AND PROCEDURE

Procedure — Judicial review — In general (§410.4601)

Judicial deference need not be given to Commissioner of Patents and Trademarks' interpretation of 35 USC 156(a), whose operative terms, individually and as combined in full definition, have common and unambiguous meaning, since deference should occur only if statutory language is ambiguous or has "left a gap," nor should deference be based upon Patent and Trademark Office's technical expertise, since significant deference is due to agency's technical expertise only if Congress has explicitly or implicitly delegated making of scientific determinations to agency, and not to interpretations resting upon narrow dissection of statutory language.

PATENTS

2. Patent grant — Patent term extension; restoration (§105.17)

Term "product" is unambiguously defined in 35 USC 156(f)(2) to mean "the active ingredient of a new drug,. . .including any salt or ester of the active ingredient," and thus only encompasses three categories of compounds—active ingredient, salt of active ingredient, or ester of active ingredient—and cannot be extended to mean any "new chemical entity," encompassing all acid, salt, or ester forms of single therapeutically active substance even if drug before being administered contained only other substances.

Appeal from the U.S. District Court for the Eastern District of Virginia, Ellis, J.; 10 USPQ2d 1100.

Action by Glaxo Operations UK Ltd. against Donald J. Quigg, Commissioner of Patents and Trademarks, challenging denial of application for patent term extension. From federal district court judgment for plaintiff, commissioner appeals. Affirmed.

Donald O. Beers, of Arnold & Porter, Washington, D.C. (Stuart J. Land, John Agar, and David E. Korn, Washington, with him on brief; Richard E. Fichter, of Bacon & Thomas, Alexandria, Va., of counsel), for plaintiff-appellee.

Irene M. Solet, Department of Justice (Stuart E. Schiffer, acting assistant attorney general, Henry E. Hudson, U.S. attorney, and John F. Cordes, with her on brief; Fred E. McKelvey, solicitor, PTO, Charles E. Van Horn, deputy solicitor, and John C. Martin, associate solicitor, of counsel), for defendant-appellant.

Before Baldwin, senior circuit judge, and Archer and Michel, circuit judges.

Michel, J.

Donald J. Quigg, Assistant Secretary of Commerce and Commissioner of Patents and Trademarks (Commissioner), appeals the Order of the United States District Court for the Eastern District of Virginia, dated February 28, 1989, granting summary declaratory judgment to Glaxo Operations U.K. Ltd. (Glaxo). *See Glaxo Operations UK Ltd. v. Quigg*, 706 F.Supp. 1224, 10 USPQ2d 1100 (E.D. Va. 1989). The court declared in its Order that Glaxo's application for patent term extension for U.S. Patent No. 4,267,320 satisfies the requirements of 35 U.S.C. §156(a) (Supp. V 1987), a provision of the Drug Price Competition and Patent Term Restoration Act of 1984 (the Act), tit. II, §201(a), 98 Stat. 1598. Because the district court correctly construed and properly applied the operative terms of the Act, we affirm.

Background

Glaxo is the assignee of U.S. Patent No. 4,267,320 ('320), issued May 12, 1981,

which claims cefuroxime axetil, an antibiotic drug. In 1985, Glaxo sought approval from the Food and Drug Administration (FDA) to market a form of this drug,[1] CEFTIN tablets, and received approval on December 28, 1987. The active ingredient of CEFTIN tablets is cefuroxime axetil. The active ingredient of CEFTIN tablets is cefuroxime axetil. The properties of this compound are such that it becomes therapeutically active and effective when orally administered. Cefuroxime axetil is an ester[2] of cefuroxime, an organic acid.

Cefuroxime and its salts[3] are claimed in Glaxo's U.S. Patent No 3,974,153. Cefuroxime and two of its salts, marketed as ZINACEF and KEFUROX, are therapeutically active antibiotics only when administered intramuscularly or intravenously. None of these compounds are effective if orally administered. FDA approved ZINACEF in 1983 and various dosage strengths of KEFUROX in 1986 and 1987, but the acid cefuroxime has not been approved.

Glaxo sought a patent term extension for its '320 patent (cefuroxime axetil) because of the lost marketing time due to the lengthy FDA review process. The Commissioner denied the extension asserting that the 1987 FDA approval of CEFTIN was not the first permitted commercial marketing or use of the "product" because ZINACEF and KEFUROX had previously been approved, and therefore the '320 patent was not eligible for a term extension under the Act. *See In re Glaxo Operations UK Ltd.*, Request for Patent Term Extension Under 35 U.S.C. 156 for U.S. Patent No. 4,267,320 (Sept. 9, 1988).

Glaxo sought declaratory and injunctive relief under the Administrative Procedures Act (APA), 5 U.S.C. §702 (1988), for which the federal district court had jurisdiction under 28 U.S.C. §1338(a) (1982). Glaxo then filed a motion for summary judgment. In responding to that motion, the Commissioner modified his grounds for rejection of Glaxo's patent term extension application. *See Glaxo,* 706 F.Supp. at 1226, 10 USPQ2d at 1102. The dispute between Glaxo and the Commissioner, however, remains focused entirely on the proper interpretation of one statutory eligibility requirement for patent term extension. Its application in this case, once properly construed, is not in dispute.

For a patent to be eligible for a term extension, among other things the product must have been "subject to a regulatory review period" and "the permission for the commercial marketing or use of the product after such regulatory review period [must have been] the *first permitted* commercial marketing or use of the *product* under the provision of law under which such regulatory review period occurred." 35 U.S.C. §156(a)(4) & (5) (Supp. V 1987) (emphasis added). Moreover, the Act explicitly defines "product" as "the active ingredient of a new drug, . . . including any salt or ester of the active ingredient. . . ." *Id.* §156(f)(2).

It is undisputed that cefuroxime axetil is the active ingredient of CEFTIN tablets. Moreover, the Commissioner does not appear to contest that ZINACEF and KEFUROX are neither salts nor esters of cefuroxime axetil. Consequently, Glaxo argues that the "product" as defined by the Act has not been previously approved or used before CEFTIN tablets were approved because neither ZINACEF nor KEFUROX fell within the definition. Accordingly, Glaxo contends that because CEFTIN is the "first permitted commercial marketing or use" of the product patented, the '320 patent is eligible for term extension.

The Commissioner, on the other hand, argues that "product" was not intended by Congress to have a literal meaning, *only* encompassing three categories of compounds: (1) an active ingredient; (2) a salt of an active ingredient; or (3) an ester of an active ingredient. He asserts that Congress intended the definition to mean any "new chemical entity," i.e., "new active moiety," which would encompass *all* acid, salt, or ester forms of a single therapeutically active substance even if the drug before being administered contained only other substances. In this case, because after being orally administered CEFTIN tablets combine with digestive substances in the human body to produce the same therapeutically active substance contained in both ZINACEF and KEFUROX, then under the Commissioner's interpretation, Glaxo has already had a prior approval of the "product" before it sought a term extension for its '320 patent.

The trial court reviewed the Commissioner's interpretation of section 156 under the standard enunciated in the APA, 5 U.S.C.

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[1] CEFTIN, as well as ZINACEF and KEFUROX, *infra,* are federally registered trademarks, Registration Nos. 1,332,796; 1,133,466; and 1,445,894, respectively.

[2] An ester is a compound derived from an acid by the exchange of a replaceable hydrogen of the latter for an organic radical, usually using an alcohol or other organic compound rich in OH groups. *See The Condensed Chemical Dictionary* 418 (G. Hawley rev. 10th ed. 1981) [hereinafter *Chemical Dictionary*].

[3] A salt is a compound formed when the hydrogen of an acid is replaced by a metal or its equivalent. *See id.* at 907.

§706(2)(A) (1988),[4] and concluded that his action was "contrary to law." Accordingly, the trial court granted Glaxo summary judgment. We hear the Commissioner's appeal under 28 U.S.C. §1295(a)(1) (1982).

OPINION

I.

In reviewing a grant of summary judgment, an appellate court must determine whether the strict standard set forth in Rule 56(c) of the Federal Rules of Civil Procedure has been satisfied. *Chula Vista City School Dist. v. Bennett*, 824 F.2d 1573, 1579 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 1042 (1988). In the instant case, both parties concede that there are no genuine issues of material fact. Consequently, this court need only decide the same question of law decided by the district court on summary judgment. That question is one of statutory interpretation, one that an appellate court can independently determine without deference to the trial court's interpretation. *See Madison Galleries, Ltd. v. United States*, 870 F.2d 627, 629 (Fed. Cir. 1989).[5]

II.

"When . . . the terms of a statute [are] unambiguous, judicial inquiry is complete, except in rare and exceptional circumstances." *United States v. James*, 478 U.S. 597, 606 (1986) (quoting *Rubin v. United States*, 449 U.S. 424, 430 (1981) (internal quotation marks omitted)). Moreover, absent a "clearly expressed legislative intention to the contrary," a statute's plain meaning "must ordinarily be regarded as conclusive." *Consumer Prod. Safety Comm'n v. GTE Sylvania, Inc.*, 447 U.S. 102, 108 (1980).

We conclude that section 156(f)(2)'s terms, "active ingredient of a new drug . . . including any salt or ester of the active ingredient," all have a plain meaning. We reach this conclusion because we must interpret statutory words as " 'taking their ordinary, contemporary, common meaning,' " unless otherwise defined by Congress. *Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1426, 7 USPQ2d 1152, 1155 (Fed. Cir. 1988) (quoting *Perrin v. United States*, 444 U.S. 37, 42 (1979)). In particular, the terms "active ingredient," "salt," and "ester" had well-defined, ordinary, common meanings when Congress enacted the Act. *See, e.g.*, 45 Fed. Reg. 72,582; 72,591 (1980); 44 Fed.Reg. 2932, 2937–38 (1979); *Chemical Dictionary, supra* note 3, at 418, 907. The Commissioner, however, suggests that Congress "inartfully" and "awkwardly" selected this combination of terms intending something other than their combined, common and ordinary meanings. Brief for Defendant-Appellant Quigg at 10, 24, *Glaxo Operations UK Ltd. v. Quigg*, No. 89–1407 (Fed. Cir. filed July 19, 1989) [hereinafter Commissioner's Brief]. This approach is unpersuasive because it simply overlooks the legal consequence that ordinarily attaches whenever statutory language has a clear and plain meaning. Instead, the Commissioner simply ignores the plain meaning of these terms and argues, as a totally unrelated question, that Congress intended a meaning contrary to the plain meaning.

Nonetheless, even when the plain meaning of the statutory language in question would resolve the issue before the court, the legislative history should usually be examined at least "to determine whether there is a *clearly expressed* legislative intention contrary to the statutory language." *Madison Galleries*, 870 F.2d at 629 (emphasis added); *see LSI Computer Sys. v. United States Int'l Trade Comm'n*, 832 F.2d 588, 590, 4 USPQ2d 1705, 1707 (Fed. Cir. 1987).[6] Consequently, although we conclude that the statutory language is unambiguous, we consider the legislative history of the Act, but only to

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[4] The APA applies to district court review of such Commissioner's decisions. *See Heinemann v. United States*, 796 F.2d 451, 454–55, 230 USPQ 430, 433 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 930 (1987); *Smith v. Mossinghoff*, 671 F.2d 533, 538, 213 USPQ 977, 982 (D.C. Cir. 1982).

[5] The standard of review is not affected by deference to agency interpretation in the instant case. *See* Section IV, *infra*.

[6] *See also United States v. American Trucking Ass'ns*, 310 U.S. 534, 544 (1940) ("[T]here certainly can be no 'rule of law' which forbids [the use of legislative history], however clear the words may appear on 'superficial examination.' ") (footnotes omitted); *National Wildlife Fed. v. Gorsuch*, 693 F.2d 156, 170 (D.C. Cir. 1982) ("In virtually every case . . . it does not end [with the statutory language] but continues with a review of the legislative history.").

Often caution requires that the legislative history be considered at least to the extent necessary to ascertain whether a contrary intent exists even when the statutory language is clear. Nonetheless, this rule of caution does not preclude, in a particular case in which the statutory language is so clear as to Congress' intent, the decision that it would be unnecessary to look further into the legislative history. *See, e.g., Brookside Veneers, Ltd. v. United States*, 847 F.2d 786, 788 (Fed. Cir.), *cert. denied*, 109 S.Ct. 369 (1988); *see Norwegian Nitrogen Prods. Co. v. United States*, 288 U.S. 294, 315 (1933).

determine whether a clear intent contrary to the plain meaning exists.

III.

Although we should consider the legislative history to ascertain whether Congress' intent was contrary to section 156(f)(2)'s plain meaning, we do not analyze this history from a neutral viewpoint. Rather, given the plain meaning, the Commissioner must provide an "*extraordinary showing* of contrary intentions." *Garcia v. United States*, 469 U.S. 70, 75 (1984) (emphasis added); *Fisons PLC v. Quigg*, 876 F.2d 99, 101, 10 USPQ2d 1869, 1870 (Fed. Cir. 1989). We conclude that no such showing has been made.

The Commissioner correctly notes that the Act has two general purposes: (1) to increase the availability of low-cost drugs by expanding a generic drug approval procedure; and (2) to further encourage new drug research by restoring some of the patent term lost while drug products undergo testing and await FDA pre-market approval. H.R. Rep. No. 857, 98th Cong., 2d Sess., pt. 1, at 14–15 [hereinafter House Report], *reprinted in* 1984 U.S. Code Cong. & Admin. News. 2647, 2647–48 [hereinafter USCCAN]. The Commissioner contends that applying the plain meaning of section 156 to patent term extension determinations will create absurd results contrary to these purposes. Although we agree that the Commissioner's interpretation of the meaning of section 156 is consistent with these *general* purposes, the plain meaning of section 156 is also consistent; the plain meaning can be said to provide exactly *how* the general objectives of the Act are to be sought. This is all the more so when, as here, the two objectives are divergent if not in outright opposition to one another. The terms Congress selected achieve a balance between the broader extensions some urged and the narrower extensions others sought and the Commissioner now advocates.

The Commissioner merely argues, via his interpretation of section 156, that fewer patents should be eligible for extensions than the plain meaning of that section suggests, and that his interpretation attains a better balance between the competing purposes of the Act. Congress, however, may decide, and here clearly did decide, how to best accommodate the conflicting objectives. Moreover, Congress clearly had articulated policy reasons for making more types of patents eligible for extension, including to encourage research. As even the Commissioner acknowledges, his interpretation would reduce the profits of brand name manufacturers who would be entitled to more limited protection from generic drug competitors than they would receive under the plain meaning interpretation of section 156. Commissioner's Brief, *supra*, at 29–30.[7] Lesser profits might result in less research on new drugs.

The Commissioner simply makes an unsupported assumption that Congress wanted to give greater emphasis to the Act's purpose of increasing generic drug availability as opposed to providing greater economic incentive to development of new patentable drugs. Congress' intent might well have been exactly the opposite of what the Commissioner suggests. More likely, it could have been a compromise between the aggressively advocated and opposing interests of brand name manufacturers versus the generic drug manufacturers.

We are reminded by the Supreme Court that:

> all legislation is not simple nor its consequences obvious or to be controlled, even if obvious. Whether there should be any legislation at all and its extent and form may be matters of dispute. Its consequences may be viewed with favor or with alarm; some regretted but accepted as inevitable — accepted as the shadow side of the good. In such situation it is for the legislature to determine, and it is very certain that the judiciary should not refuse to execute that determination from its view of some consequence which . . . may have been contemplated and appreciated when the act was passed, and considered as overbalanced by the particular advantages the act was calculated to produce. . . . "It would be dangerous in the extreme, to infer from extrinsic circumstances, that a case for which the words of an instrument expressly provide, shall be exempted from its operation."

Pirie v. Chicago Title and Trust Co., 182 U.S. 438, 451–52 (1901) (quoting *Sturgis v. Crowninshield*, 17 U.S. (4 Wheat.) 122, 202 (1819)). We simply cannot say that the plain meaning of section 156 would provide unwanted results because Congress may very well have contemplated all the ramifications of its chosen definition in light of the political realities as seen played out in the legislative process, and we must assume it did.

Further, we are hesitant to stray from the plain meaning of the statute because both the terms Congress used and the terms the

[7] Normally, utility patent terms last seventeen years. 35 U.S.C. §154 (1982). Under the Commissioner's interpretation, any part of the term lost to FDA review would not be restored for certain patents, thereby shortening the effective patent life.

Commissioner would have us substitute were all well-known and well-defined at the time the Act was passed.[8] Nevertheless, Congress chose particular terms — "active ingredient, . . . including any salt or ester of an active ingredient. . . ." Accordingly, we can infer that in so choosing, Congress may have deliberately rejected the very terms the Commissioner asserts were the intended meaning of section 156.

Besides asserting that to accept the common meaning of section 156's terms compromises the general purposes of the Act, the Commissioner cites specific language in the House Report as evidencing Congress' contrary intent:

> The Committee's bill requires extensions to be based on the first approval of a product because the only *evidence available to Congress* showing that patent time has been lost is data on so-called *class I, new chemical entity drugs.* These drugs had been approved by the Food and Drug Administration (FDA) for the first time.

House Report, *supra,* at 38 (emphasis added), *reprinted in* USCCAN, *supra,* at 2671. The Commissioner notes that this Report describes the House bill which, without amendment, became section 156, and that the House Report specifically refers to the FDA classification system by using the terms "class I, new chemical entity drugs." The Commissioner argues that this language shows Congress' intent that "product" was to mean "new chemical entities" as defined by FDA.[9] We are unpersuaded because although the Commissioner's construction may provide an equally admirable result, we see this House Report language as ambivalent as to Congress' intended meaning for "product." The House Report language, including the phrase "evidence available," can just as well be read as giving an historical description of how the problem addressed by the bill came to light, as opposed to exactly how the problem was to be resolved; we simply cannot find any clear statement that extensions are required based on first approval of "new chemical entities." In fact, if that were Congress' intent, one would expect it to use the same term — "new chemical entity" — in the bill as is used in the House Report. Instead, the bill employed other terms with an equally clear but quite different meaning.

Additionally, the Commissioner quotes two floor statements by sponsors of the bill resulting in the Act as also evidencing Congress' intent that "product" mean "new chemical entities." *See* 130 Cong. Rec. 24,425 (1984) (Rep. Waxman); *id.* at 23,765 (Sen. Hatch). Although we acknowledge that the sponsors' remarks — which, like the House Report, refer to "new chemical entities" — should be afforded some weight as to the meaning of the bill, we are equally reminded by the Supreme Court that "[o]ral testimony of . . . individual Congressmen, *unless* very precisely *directed* to the intended meaning of *particular words in a statute,* can seldom be expected to be as precise as the enacted language itself." *Regan v. Wald,* 468 U.S. 222, 237 (1984) (emphasis added). These statements, however, were not precisely directed to the definition of "product." First, these statements could very well have been simply the sponsors' shorthand simplification for the technical language, "active ingredient . . . including any ester or salt of the active ingredient. . . ." Second, they were both directed toward a different title of the Act than the one at issue in this appeal. Consequently, we cannot say that these statements provide a clearly expressed contrary intent that section 156's terms not be afforded their ordinary meaning.

IV.

In construing this Act, we must consider whether deference is due the Commissioner's interpretation of the intended meaning of section 156. The Commissioner asserts a number of reasons why this court should defer.

[1] First, the Commissioner argues, broadly, that this court must defer to his statutory interpretation provided it is "reasonable," and not clearly contrary to Congress' intent, citing, inter alia, *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.,* 467 U.S. 837, 842–43 (1984), and *Chemical Manufacturers Association v. Natural Resources Defense Council, Inc.,* 470 U.S. 116, 126 (1985). The Commissioner's position is

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[8] *See, e.g.,* 45 Fed. Reg. 72,582; 72,591 (1980); 44 Fed. Reg. 2932; 2937–38 (1979); *Chemical Dictionary, supra* note 3, at 418, 907; FDA, Bureau of Drugs, *Staff Manual Guide BD 4820.3,* at 1–2 (Feb. 19, 1982).

[9] FDA classifies drugs into six chemical types. One such type is defined:

> *Type 1* — New molecular entity — i.e., the active moiety is not yet marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product.

FDA, Bureau of Drugs, *Staff Manual Guide BD 4820.3,* at 1–2 (Feb. 19, 1982). The Commissioner's interpretation is further questionable because the House Report refers to "Class I" and "new chemical entity" rather than the FDA's term "Type 1" and "new molecular entity."

untenable, however, because he has mistaken the applicability of those cases to the instant case. The rule of deference enunciated in those cases is limited to when the statutory language has "left a gap" or is ambiguous. *See Chevron,* 467 U.S. at 842–44; *Chemical Manufacturers,* 470 U.S. at 126. Here, as we have already stated, section 156(f)(2)'s operative terms, individually and as combined in the full definition, have a common and unambiguous meaning, which leaves no gap to be filled in by the administering agency. Accordingly, we need not defer to any reasonable interpretation of the Commissioner.

Additionally, the Commissioner asserts that deference is due a contemporaneous construction of the agency charged by Congress with implementing the new statute. Often cited by the Supreme Court as well as this court, *see, e.g., Chevron,* 467 U.S. at 844 n.14; *Chula Vista,* 824 F.2d at 1580, this doctrine has been applied when the statutory language is "doubtful and ambiguous" and the agency's construction is soon after the statute's enactment when the circumstances surrounding its enactment were well known. *See Edwards' Lessee v. Darby,* 25 U.S. (12 Wheat.) 206, 210–11 (1827); *Smith-Corona Group v. United States,* 713 F.2d 1568, 1576 & n.24, 1 Fed. Cir. (T) 130, 138 & n.24 (1983). Here, the situation is quite different. First, section 156(f)(2) is unambiguous on its face. Second, whether the Commissioner's construction was contemporaneous is questionable; his interpretation was neither applied nor publicly announced until nearly four years after the date of enactment of the Act, September 24, 1984. *Compare Illinois Commerce Comm'n v. Interstate Commerce Comm'n,* 749 F.2d 875, 881 (D.C. Cir. 1984) (final agency interpretation of statute two years after being passed not considered contemporaneous), *cert. denied,* 474 U.S. 820 (1985), *with Zenith Radio Corp. v. United States,* 437 U.S. 443, 450 (1978) (deference accorded agency interpretation formed within one year of statute's enactment).

Finally, the Commissioner asserts that his interpretation must be accorded deference because this case involves "highly technical, scientific questions within the agency's special expertise." Commissioner's Brief, *supra,* at 15. Once again the Commissioner describes a rule of jurisprudence which is inapposite to this case. Significant deference is due to an agency's technical expertise when Congress has explicitly or implicitly delegated to the agency the making of scientific determinations. *See, e.g., Industrial Union Dep't, AFL-CIO v. American Petroleum Inst.,* 448 U.S. 607, 642, 656 (1980). But when "the interpretation rests not on policy considerations but on a narrow dissection of statutory language, the courts are equally skilled in making such an interpretation, and reduced deference is owed." *Illinois Commerce Comm'n,* 749 F.2d at 882 n.10.

In the instant case, Congress qualified its express authorization to the Commissioner to determine whether patents are eligible for extension, *see* 35 U.S.C. §156(e)(1) (Supp. v. 1987), by providing an explicit and precise definition of "product" in section 156(f)(2), using well-established scientific terms. Although the definition does involve technical subject matter, Congress specifically selected terms with narrow meanings that it chose from among many alternatives.[10] Congress could have, but did not, select broad terms with a range of possible meanings. If it had, Congress could be said to have implicitly delegated discretion to the Commissioner to use his scientific expertise to determine what further definition would best carry out the purpose of the Act.[11] Here, all Congress left to the Commissioner's technical expertise was determining *whether* any patented chemical compound named in a patent term extension application fell within the statutory definition of "product," but *not what* "product" was to mean. Consequently, we will give great deference to the Commissioner's determinations as to which patented chemical compounds fall within Congress' definition of "products," but little or no deference to the Commissioner's surmise of Congress' intent in framing its definition.

Conclusion

[2] We cannot say whether the meaning the Commissioner ascribes to section

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[10] For example: "new molecular entity," "active moiety," or "new chemical entity."

[11] The FDA also has administrative duties under the Act. However, as opposed to title II of the Act, that applies to the Patent and Trademark Office, title I applies to the FDA. Title I includes language similar to the section 156 language in dispute in this appeal. *See* 21 U.S.C. §§355 (j) (4) (D) (i) & (v) (Supp. V 1987). The Commissioner attempts to bootstrap his claim of deference by emphasizing that the FDA has interpreted the nearly identical language of title I in a similar manner. He stresses that the FDA similarly has technical expertise. We are unpersuaded. First, the FDA's interpretation, like the Patent and Trademark Office's, may be based on its own judgment of what is better policy. Second, the FDA's interpretation of plain statutory terms is as unlikely to require technical expertise and technical judgment as is the Commissioner's.

156(f)(2) would provide a better balanced policy for patent term extensions. Nevertheless, that is not the issue before this court. Striking balances in legislative language is Congress' job. Here Congress utilized its constitutional powers vigorously, providing precise statutory definitions. We may only decide whether Congress has *clearly* expressed elsewhere an intent contrary to the plain meaning of the statutory terms. That, we are unable to do. Accordingly, the plain meaning of the statutory language must stand as Congress' intent and be honored by both the courts and the Patent and Trademark Office. The judgment of the district court is therefore

AFFIRMED.

Court of Appeals, Ninth Circuit

Bibbero Systems Inc. v. Colwell Systems Inc.

Nos. 88-1925, 88-2440

Decided January 12, 1990

COPYRIGHTS

1. Non-copyrightable matter — Blank forms (§211.03)

Blank medical insurance claim forms, known as "superbills," which doctors use to obtain reimbursement from insurance companies and which contain instructions to patient for filing insurance claims, boxes for patient information, clauses assigning insurance benefits and authorizing release of patient information, and checklists to be filled out by doctor to indicate diagnosis and services performed, are blank forms which are not copyrightable pursuant to 37 CFR 202.1(c), since "superbill" simply gives doctors convenient method for recording services performed and conveys no information about patient, diagnosis, or treatment until it is filled out, nor can "superbill" be copyrightable under "text with forms" exception to blank forms rule, since instructions provided are far too simple to be copyrightable as text in and of themselves.

2. Infringement pleading and practice — Relief and damages — Costs and attorney's fees (§217.1105)

Copyright infringement defendant who prevailed when plaintiff's medical insurance claim forms were held to be non-copyrightable blank forms is not entitled to award of attorney's fees under 17 USC 505, since defendant has failed to show, as required for award of fees to prevailing defendant, that action was frivolous or brought for harassment, in view of conflicting precedent regarding blank forms rule; fact that defendant prevailed on summary judgment does not waive requirement to show frivolousness or bad faith.

Appeal from the U.S. District Court for the Northern District of California, Henderson, J.

Action by Bibbero Systems Inc. against Colwell Systems Inc., for copyright infringement. From federal district court decision granting summary judgment to defendant, but denying its request for attorney's fees, parties cross-appeal. Affirmed.

Anthony B. Diepenbrock, Katherine C. Spellman, and John A. Hughes, San Francisco, Calif., for Bibbero Systems Inc.

Matthew D. Powers, of Orrick, Herrington & Sutcliff, San Francisco, for Colwell Systems Inc.

Before Goodwin, chief judge, and Pregerson and Reinhardt, circuit judges.

Goodwin, C.J.

This case requires us to examine the scope of the blank forms rule, 37 C.F.R. §202.1(c) (1982), which provides that blank forms are not copyrightable. Plaintiff Bibbero Systems, Inc. (Bibbero) contends that Colwell Systems, Inc. (Colwell) infringed upon its copyright by duplicating its medical insurance claim form. The district court granted summary judgment to Colwell, finding that the billing form was an uncopyrightable blank form designed for recording information. On cross-appeal, Colwell argues that the district court erroneously denied its request for attorney's fees. We have jurisdiction under 28 U.S.C. §1291, and we affirm.

Bibbero designs and markets blank forms known as "superbills" which doctors use to obtain reimbursement from insurance companies. Each superbill contains simple instructions to the patient for filing insurance claims; boxes for patient information; simple clauses assigning insurance benefits to the doctor and authorizing release of patient information; and two lengthy checklists for the doctor to indicate the diagnosis and any services performed, as well as the applicable fee. All entries on the checklists are categories specified by the American Medi-

vapour /'veîp...(r)/ *n. & v.*
(*US* **vapor**)
_*n.*
1 moisture or another substance diffused or suspended in air, e.g. mist or smoke.
2 *Physics* a gaseous form of a normally liquid or solid substance (cf. GAS).
3 a medicinal agent for inhaling.
4 (*in pl.*) *archaic* a state of depression or melancholy thought to be caused by exhalations of vapour from the stomach.
_*v.intr.*
1 rise as vapour.
2 make idle boasts or empty talk.
□ **vapour density** the density of a gas or vapour relative to hydrogen etc. **vapour pressure** the pressure of a vapour in contact with its liquid or solid form. **vapour trail** a trail of condensed water from an aircraft or rocket at high altitude, seen as a white streak against the sky.
□□ **vaporous** *adj.* **vaporously** *adv.* **vaporousness** *n.* **vapourer** *n.* **vapouring** *n.* **vapourish** *adj.* **vapoury** *adj.*

Etymology ME f. OF *vapour* or L *vapor* steam, heat[1]

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[1]"The Concise Oxford Dictionary," *Microsoft® Encarta® 97 Encyclopedia.* The Concise® Oxford Dictionary, 8th Edition. (c) © Oxford University Press. All rights reserved.

US005167242A

United States Patent [19]

Turner et al.

[11] Patent Number: 5,167,242

[45] Date of Patent: Dec. 1, 1992

[54] NICOTINE-IMPERMEABLE CONTAINER AND METHOD OF FABRICATING THE SAME

[75] Inventors: James E. Turner, Atascosa; Michael P. Ellis; Ronald G. Oldham, both of San Antonio, all of Tex.; Ira Hill, Locust, N.J.; Bengt E. Malmborg, Helsingborg; Sven-Börje Andersson, Ödåkra, both of Sweden

[73] Assignee: Kabi Pharmacia Aktiebolaq, Sweden

[21] Appl. No.: 535,967

[22] Filed: Jun. 8, 1990

[51] Int. Cl.[5] A24F 47/00

[52] U.S. Cl. 131/273; 131/337; 131/359; 128/202.21; 128/203.21; 128/204.13

[58] Field of Search 131/329, 336, 337, 335, 131/359; 128/270, 273, 200.14, 200.19, 200.21, 202.21, 203.12, 203.15, 203.21, 203.23, 204.11, 204.13; 206/242; 222/5, 87, 81, 92

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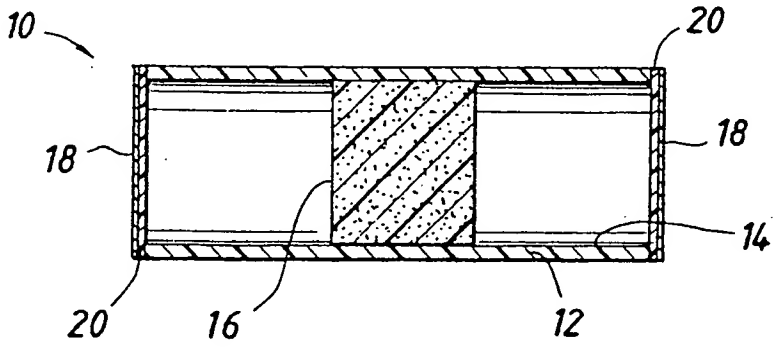
Primary Examiner—Vincent Millin
Assistant Examiner—J. Doyle
Attorney, Agent, or Firm—Pravel, Gambrell, Hewitt, Kimball & Krieger

[57] ABSTRACT

The present invention relates to a nicotine-impermeable container and a method for fabricating same. Additionally, the invention relates to a nicotine inhaling device which allows a user to ingest nicotine vapors orally. The nicotine inhaling device of the present invention is primarily directed to a device which can be used as a smoking cessation aid.

23 Claims, 2 Drawing Sheets



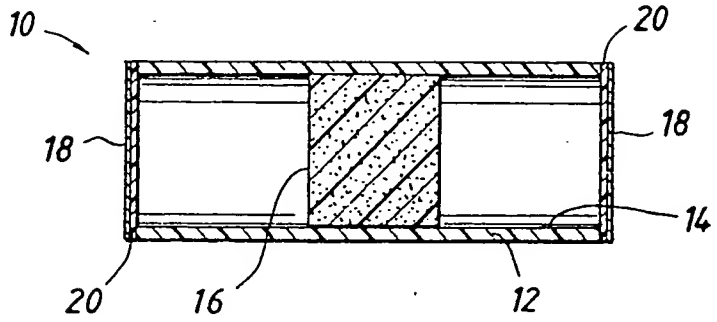


FIG. 1

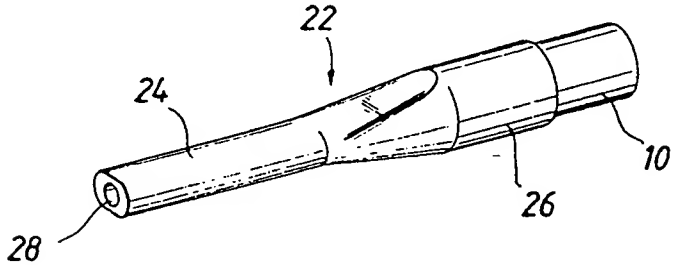


FIG. 2

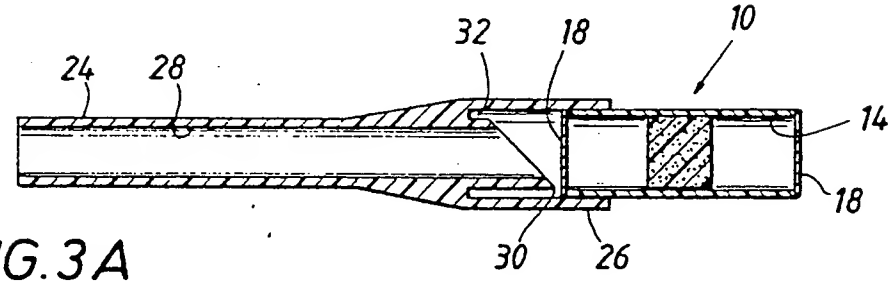


FIG. 3A

FIG. 3

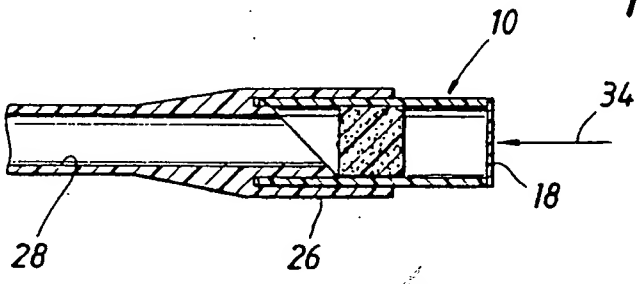


FIG. 3B

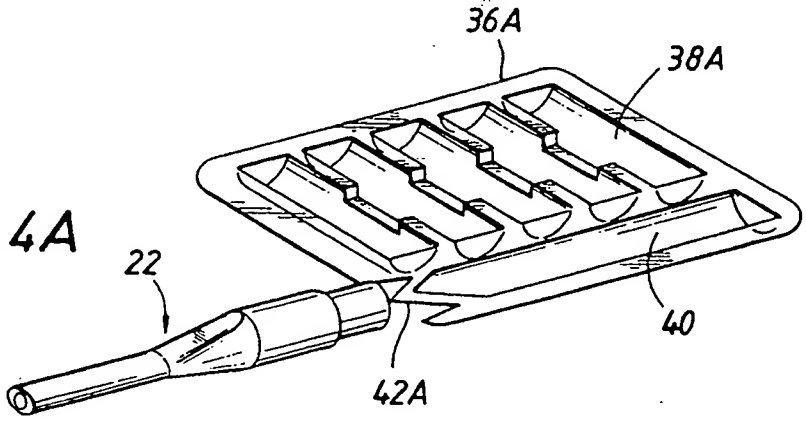


FIG. 4A

FIG.4B

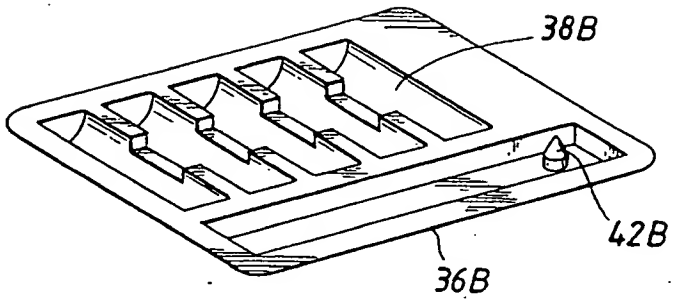


FIG.5A

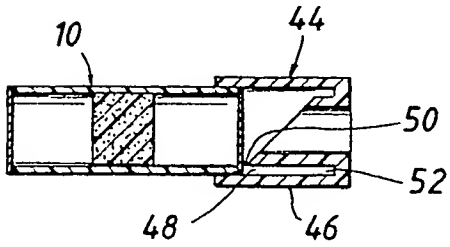
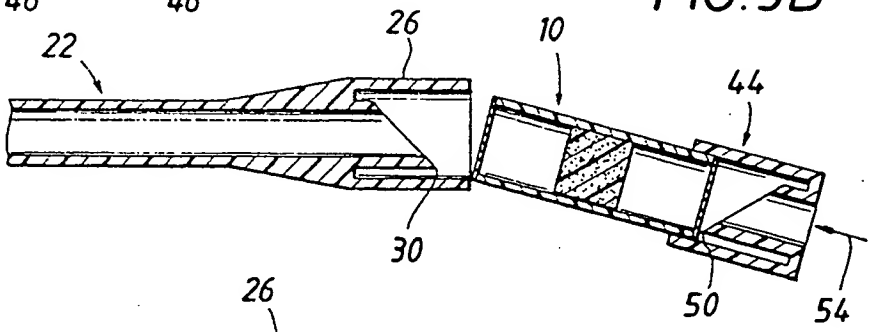


FIG.5B

FIG.5



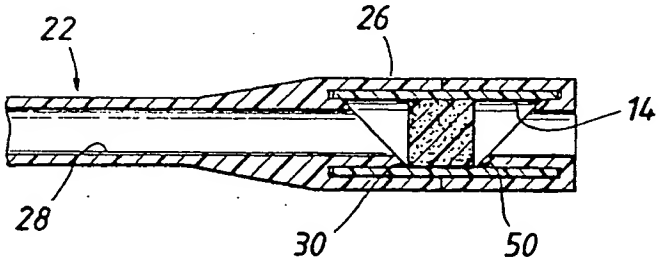


FIG.5C

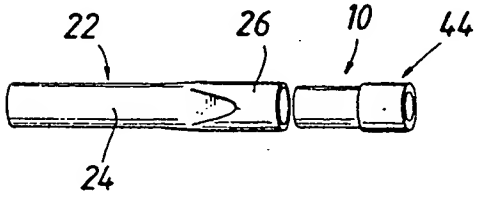


FIG.6

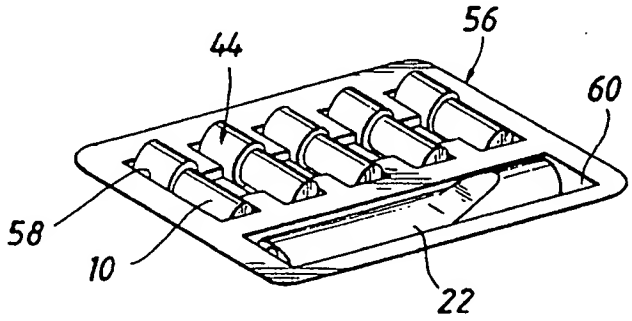


FIG.7

NICOTINE-IMPERMEABLE CONTAINER AND METHOD OF FABRICATING THE SAME

FIELD OF THE INVENTION

The present invention relates to a nicotine-impermeable container and a method for fabricating same. A preferred embodiment of the invention is a nicotine inhaling device which allows a user to ingest nicotine vapors orally and is primarily used as a smoking cessation aid.

BACKGROUND OF THE INVENTION

Evidence has been mounting over the years linking many diseases such as high blood pressure and lung cancer to cigarette smoking. The U.S. Surgeon General's report of 1988 on the health consequences of smoking estimated that in the United States alone about 300,000 deaths are caused each year by cigarette-related diseases. Indeed, excessive smoking is now recognized as one of the major health problems throughout the world.

Because of the addictive nature of nicotine, it is extremely difficult for a heavy smoker to stop smoking completely. Even though nicotine is one of the risk factors in tobacco smoke, other substances formed during the combustion of tobacco such as carbon monoxide, tar products, aldehydes and hydrocyanic acid are considered to be even greater risk factors.

Because of the addictive nature of nicotine, an acceptable alternative to smoking has been to provide nicotine in a form or manner other than by smoking. Several products have been developed that accomplish this result. The most successful product which is used as a smoking substitute and/or a smoking cessation aid is a chewing gum known as Nicorette ® which contains nicotine as one of its active ingredients. This product is the only form of nicotine replacement which has been approved by the Food and Drug Administration to date.

In this chewing gum, nicotine is present in the form of a complex with an insoluble cation-exchanger (polacrilex) which is disbursed in a gum base. A buffering agent is included in this composition. U.S. Pat. Nos. 3,877,486; 3,901,248; and 3,845,217 are directed to this product.

Another product generally developed in this field is a smokeless cigarette sold under the trademark Favor which was on the United States market for about 18 months. This product was subsequently withdrawn because it did not satisfy the Food and Drug Administration requirements. Various embodiments of this product are described in U.S. Pat. Nos. 4,284,089; 4,800,903; and 4,813,437.

This product generally allows nicotine to be inhaled through an elongated tube in which a porous polymer reservoir containing nicotine free base is mounted. An air stream caused by suction from the user carries nicotine vapors into the lungs of the user to satisfy a nicotine craving.

In commercial embodiments of this product, the tube was formed of polybutyleneterephtalate (PBTP) and polyethylene (PE) polymers. This tube was wrapped in a polyehtyleneterephthalate (PET) wrapper in order to seal the nicotine from the atmosphere. However, it was unexpectedly found that the nicotine free base migrated through the packaging material and rapidly disappeared from the system because the material was more permeable than anticipated. It has been estimated that the shelflife of the unrefrigerated vapor inhaler was approximately one month.

The present invention concerns an improvement of the container for holding the nicotine free base, thereby improving the shelf-life and purity of the nicotine stored.

SUMMARY OF THE INVENTION

In order to solve the problems discussed above, in a preferred embodiment of the invention, a container in the form of a cartridge for a nicotine inhaler includes a cartridge housing and a passageway in the housing in which a nicotine reservoir is located. The reservoir is designed to hold a measured amount of nicotine in a form that will allow nicotine vapor to be released into a fluid stream passing around or through the reservoir. The passageway has at least two openings communicating outside the housing for allowing a fluid stream through the passageway. The reservoir is sealed from the atmosphere by a nicotine-impermeable barrier which includes passageway barrier portions for sealing the passageway on both sides of the reservoir with at least these barrier portions being penetrable for opening the passageway to the atmosphere.

In the embodiment of the invention in which the cartridge is a cylinder, the passageway is defined by the inner surface of the cylinder with openings at both ends. The nicotine reservoir can be in the form of a polymer plug in which a nicotine free base is applied. In order to seal the reservoir from the atmosphere, the tube or cylinder can be formed of a material that is impermeable to oxygen, nitrogen and nicotine, such as a copolymer of acrylonitrile and methyl acrylate. An example of this material is manufactured by B.P.-Sohio under the trade name Barex. Aluminum foil coated with Barex could also be used.

The openings in the cylinder are sealed by a thin aluminum foil or other type of flexible, penetrable, material that is impermeable to oxygen, nitrogen and nicotine. In order to provide an easy means for sealing the aluminum foil to the ends of the cylinder, the foil can be coated on its inner surface with a thin layer or film of Barex and the composite can be heat sealed to the ends of the cylinder for forming the passageway barrier portions.

In order to protect the nicotine in the reservoir from degrading in the presence of oxygen, the reservoir can be inserted in the tube in an oxygen-free environment and filled with an inert gas such as nitrogen. One way of accomplishing this result is to load the nicotine reservoir in the tube in a nitrogen atmosphere and then sealing the Barex-covered aluminum foil pieces to the ends of the tube. Barex and aluminum have been chosen as the materials to use because they exhibited negligible penetration of nicotine during the shelf-life period and Barex is a good heat sealing material.

When the inhaler is ready to be used, it can be placed in a specially designed mouthpiece which has a receiving end surrounding the passageway with a sharp tip adjacent the passageway in the mouthpiece for penetrating one end of the cylinder when it is inserted into the receiving end. The other end of the cylinder can be penetrated by any suitable means such as, for example, a sharp object in the form of a knife or a holder especially designed to fit over the other end of the tube with a sharpened tip around an opening that leads to the

atmosphere. After the cartridge is inserted into the mouthpiece and both ends are penetrated, the user is able to suck on the mouthpiece and receive a satisfactory dose of nicotine vapor to satisfy his or her craving.

The cartridges can be sold in dispensing kits containing a number of cartridges along with a single mouthpiece. In the embodiment where the outer end of the cartridge needs to be penetrated by an object other than a part of the inhaler, the dispensing container can include a sharpened edge for easy use.

The invention can be applied to other embodiments where nicotine needs to be stored, in a container which provides easy access to the user, for long periods of time before it is used.

In order to receive a complete understanding of the invention, the detailed description of exemplary embodiments set forth below should be considered in conjunction with the accompanying drawings, in which:

FIG. 1 is a sectional view of a cartridge of the present invention in which a nicotine reservoir is located;

FIG. 2 is a perspective view of the cartridge of FIG. 1 inserted into a mouthpiece;

FIG. 3 is a sectional view of the cartridge of FIG. 1 in the end of the mouthpiece of FIG. 2, FIG. 3A showing the cartridge ready to be inserted to penetrate the foil at one end of the cartridge, and FIG. 3B showing the cartridge fully inserted into the mouthpiece;

FIGS. 4A-B are perspective views of a dispensing kit with a sharpened edge for the cartridge and mouthpiece shown in FIGS. 1-3;

FIGS. 5A-C are sectional views that show the cartridge of FIG. 1 being inserted into a mouthpiece with the outer end being penetrated by an outer end cap portion of the mouthpiece;

FIG. 6 is a perspective view of the embodiment shown in FIG. 5; and

FIG. 7 is a perspective view of a dispensing kit of the embodiment of the invention shown in FIGS. 5 and 6.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Referring to the drawings, exemplary embodiments of the invention will be described in detail. FIG. 1 shows cartridge **10**, in accordance with the invention, which is formed of a cylindrical body **12** that defines a passageway **14** through which a stream of fluid such as air can travel. A reservoir **16** is mounted within the passageway **14** for holding nicotine free base for the reasons discussed below. The reservoir **16** can be formed of a porous polymer plug or other suitable materials such as described in U.S. Pat. Nos. 4,284,089; 4,800,903; and 4,813,437, the contents of such patents being incorporated by reference as though fully set forth herein. These three patents are now owned by the entity which owns the invention described in this patent application.

For the purposes of the invention as described, the reservoir is formed of porous polyethylene in which a thin layer of liquid nicotine has been distributed. Details of the porous plug and its operation and the composition of nicotine are described in greater detail in U.S. Pat. No. 4,800,903.

For the purposes of this invention, the polyethylene plug can be charged with a mixture of nicotine, menthol, and ethanol. The weight ratio of nicotine to menthol to ethanol is preferably about 10:1:120. A weight ratio of 10:1:160 has additionally been tested and proved to function well. As an example, the composition of the loading solution for approximately 150,000 polyethylene plugs is made up of 18,000 grams of ethanol, 1,500 grams of nicotine, and 150 menthol. A given amount of ethanol is placed in a mixing vessel (not shown) and the menthol is added and stirred until it is completely dissolved.

Nicotine is then added through the solution and agitated manually for about three minutes. A tight fitting lid is then placed on the mixing vessel. The temperature of cooling water in a condenser (not shown) is then adjusted to 14° C. and circulated at a volume of 10 liters/minute. A jacketed vacuum drier (not shown), with an inner volume of 260 liters, has water circulated through the jacket at a temperature of 20 ±1° C. at a volume of 5 liters/minute. The plugs are placed into the vacuum drier and the vessel is evacuated to less than −27 inches of mercury.

The nicotine/ethanol solution is sucked by the aid of the under pressure into the vacuum drier. The vacuum valve is then shut. The vacuum should be less than 20 inches of mercury. The vacuum drier is then rotated at a speed of 4 revolutions per minute for 10 minutes. The vacuum pump is then started and vacuum valve opened and the temperature on the inlet water to the vacuum drier is raised to 40°±1° C. The vacuum drier and pump should operate until a temperature differential of 5-6° is reached between the inner temperature of the vacuum drier and the inlet water to the same drier. A Kinney High Vacuum Pump Model KC-8 was utilized in the above-described procedure.

When the temperature differential mentioned above is reached, the vacuum drier and pumps are stopped. The vacuum drier is then filled with nitrogen and the polyethylene plugs are unloaded into a specially designed container which is evacuated to a pressure of minus 28 inches of mercury and then refilled with nitrogen. This procedure is then repeated to make sure all of the oxygen has been removed from the system. The nitrogen-loaded polyethylene plugs are then kept in a bulk container filled with nitrogen to protect the nicotine against oxygen. The plugs are then inserted into suitable tubes in a nitrogen atmosphere and sealed as discussed below.

In order to prevent oxygen from migrating into the cartridge **10** after it is fabricated and to prevent the nicotine from migrating out of the cartridge **10**, the cylindrical body **12** is formed of a nicotine-impermeable material. A suitable material found for this purpose is a copolymer of acrylonitrile and methacrylate sold under the trade name Barex ® by B.P.-Sohio.

A variety of compounds had been tested for use as nicotine-impermeable materials. Initially, it was believed that crystalline polymers, due to the small nature of their interstitial spaces, would make good candidates. However these compounds were found to be ineffective in deterring nicotine migration. Unexpectedly, Barex proved to be an effective material even though it is an amorphous polymer.

Barex is particularly suited to the application described since it is heat sealable to provide a nicotine-impermeable barrier at the seal and is composed of ingredients which are permissible for use as an adhesive under the provisions of F.D.A. Regulation 21 CFR 175.105. Barex can also be adhered to aluminum or other metal foils so that a suitable nicotine-impermeable package can easily be formed by heat sealing adjacent layers of Barex film with the aluminum foil as a backing for one or more layers.

For the embodiment of FIG. 1, in order to maintain the inert gas in the tube after the reservoir 16 has been inserted, both ends of the tube are covered with a nicotine-impermeable barrier such as a layer of aluminum foil 18. The foil layers are sealed to the Barex tube 12 through a layer of Barex 20 adhered to the foil 18 so that the layers of foil 18 can easily be sealed to the ends of the Barex tube 12 through the application of heat. While the Barex is adhered to the aluminum foil by the use of a suitable adhesive, such adhesives cannot be used to seal the layers of Barex together or the aluminum foil to the Barex since such adhesives are not themselves nicotine-impermeable and the nicotine will migrate through the seal itself.

A cartridge 10 of the type described above can be used in conjunction with a mouthpiece 22 as shown in FIG. 2. By forming the cylindrical body 12 of Barex and using pieces of Barex-coated aluminum foil to form the passageway barrier portions, the nicotine free base charged into the reservoir 16 is prevented from migrating out of the cartridge 10 by inserting and maintaining the nicotine-containing reservoir 16 in an oxygen-free environment. For example, by charging the cartridge 10 with an inert gas such as nitrogen, degradation through interaction with oxygen of the nicotine free base is prevented. In this way, a fully effective dose of nicotine is available for the user upon penetration of the pieces of foil 18 as described below.

Alternatively to the construction described above, the nicotine-impermeable barrier can be formed in other ways. For example, the tube could be formed of PE or other types of rigid materials with a layer of Barex adhered to the inner surface of the tube. Instead of having a tube, a reservoir could be formed with openings in either end with the reservoir coated entirely with a layer of Barex with the ends being penetrable as discussed. Other suitable cartridges could also be formed in accordance with the invention as long as the nicotine is isolated from the atmosphere by means of a nicotine-impermeable barrier and the barrier is penetrable to release the nicotine when desired.

As shown in FIG. 2, a mouthpiece 22 can be used which includes a mouth engaging portion 24 and a cartridge holder 26. A passageway 28 is formed to extend from the mouth engaging portion 24 through to cartridge holder 26.

As shown in FIGS. 3A and 3B, in order to mount the cartridge 10 in the mouthpiece 22, the cartridge 10 is placed in the outer end of the cartridge holder 26, adjacent to a sharpened tip 30 which is formed around the portion of the passageway 28 that communicates with the cartridge holder 26. The sharpened tip 30 is in the form of a cylindrical section cut at an angle so that a cylindrical space 32 is formed between the outer surface of the sharpened tip and the inner surface of the cartridge holder 26 to receive a portion of the cylindrical body 12 as the cartridge 10 is pushed into place to the position shown in FIG. 3B in the direction of arrow 34.

The inner surface of the cartridge holder 26 and the cartridge 10 are designed so that when the cartridge 10 is in the position shown in FIG. 3B, the cartridge 10 is held in place by the cylindrical wall which forms the cartridge holder 26. By pushing the cartridge in the direction of the arrow 34, the pointed tip 30 operates to penetrate the aluminum foil layer 18 on the inner end of the cartridge 10 and expose it to the passageway 28 of the mouthpiece 22.

In order to allow air to flow through the cartridge 10 and pass by or through the reservoir 16, the nicotine-impermeable layer 18 on outer end of the cartridge 10 must also be penetrated. This can be done by any sharp object such as a knife or the like. However, one way of providing an easily-usable sharpened object is to provide dispensers 36A-B of the type shown in FIGS. 4A-B which are formed of molded plastic and contain a number of compartments 38A-B for receiving cartridges 10 (not shown). In FIG. 4A, a tray 40 is also provided for holding a mouthpiece 22. All of these components can be shrink wrapped in a transparent plastic and used as a sales package.

In order to provide a handy sharpened object for penetrating the foil layer 18 over the outer end of the cartridge 10, a sharpened tip 42A-B can be provided. In this way, after a cartridge 10 is inserted into the end of the mouthpiece 22 and pushed to the position shown in FIG. 3B, the outer end can be penetrated simply by pushing it against the sharpened tip 42A-B as shown, for example in FIG. 4A. In this way, the passageway 28 communicates with the atmosphere through the passageway 14 of the cartridge 10 so that the user can suck on the mouth engaging end 24 of the mouthpiece 22 in order to receive nicotine vapor as described.

An alternative to using a sharpened tip to penetrate either or both foil ends is to form the foil with a portion that can be grasped (not shown) and then having the user peel the foil layer 18 off the cartridge 10.

Another embodiment of the invention is shown in FIGS. 5 and 6 where a cartridge 10 of the same configuration described above is used in conjunction with a cartridge penetrator/cover 44. As shown in FIG. 5A, the penetrator/cover 44 is inserted over the outer end of the cartridge 10 and the combination is then inserted into the outer end of the cartridge holder 26 of the mouthpiece 22 similar to the one shown in FIGS. 2 and 3.

The cartridge penetrator/cover is formed of a cylinder 46 which defines a passageway 48, the outer end of which is defined by a cylindrical sharpened tip 50 which is similar in design to the sharpened tip 30 in the cartridge holder 26. An annular space 52 is formed between the outer surface of the sharpened tip 50 and the inner surface of the cylinder 46 for receiving the cylindrical body 12 of the cartridge 10.

After the penetrator/cover 44 is placed over the outer end of the cartridge 10, it is pushed toward the position shown in FIG. 5 in the direction of arrow 54 (FIG. 5B) so that the sharpened tip 50 operates to penetrate the foil layer 18 located over the outer end of the cartridge 10. In this way, the passageways 28 of the mouthpiece 22 and 14 of the cartridge 10 communicate with each other and with the atmosphere so that the user is able to suck on the mouthpiece and receive the nicotine vapor as described above.

The embodiment of the invention shown in FIGS. 5 and 6 can be packaged in a manner shown in FIG. 7 where a molded plastic tray 56 includes a number of compartments 58 designed to hold a cartridge and cartridge penetrator/cover 44 in the non-penetrating position shown in FIG. 5A. A compartment 60 can also be provided to hold a mouthpiece 22 with all of the elements being packaged by shrink wrapping them in transparent plastic (not shown).

By providing the inhaler described above, a cartridge for holding nicotine to be used in conjunction with the mouthpiece can be marketed without losing its effec-

tiveness through an unnecessarily short shelf-life. By providing a cartridge with a nicotine-impermeable barrier, nicotine is prevented from migrating out of the cartridge and the dosage initially provided is maintained throughout the life of the product. Further, by maintaining and storing the nicotine reservoir in an oxygen-free atmosphere, the nicotine is prevented from degrading through the interaction with the oxygen and the effective level of the nicotine dose is maintained.

The foregoing description is not intended to be limiting in nature and the invention is intended to include all improvements and variations beyond those specifically described, which fall within the spirit and scope of the appended claims.

What is claimed is:

1. A cartridge for a nicotine inhaler, comprising:
a) a cartridge housing;
b) a passageway in said cartridge housing;
c) a nicotine reservoir in said passageway for holding a measured amount of nicotine in a form that will allow nicotine vapor to be released into a fluid stream passing around or through the reservoir;
d) said passageway comprising at least two openings communicating outside said housing for allowing a fluid stream to pass through said passageway;
e) said nicotine reservoir being sealed from the atmosphere and maintained in an effectively oxygen-free environment by a nicotine-impermeable barrier which includes passageway barrier portions for sealing the passageway on both sides of the reservoir, at least one said passageway barrier portions being penetrable for opening said passageway to the atmosphere; and
f) said passageway further having a portion inside said passageway barrier portions that is filled with inert gas.

2. The cartridge of claim 1, wherein the cartridge housing is an elongated member, the passageway being defined by the inner surface on the member and the passageway openings being located on opposite ends of the member.

3. The cartridge of claim 2, wherein the elongated member is cylindrical in shape.

4. The cartridge of claim 2 in combination with a mouthpiece, said mouthpiece comprising:
a) an elongated passageway section with openings at both ends;
b) one end of the passageway section adapted to be received in the mouth of the user;
c) the other end of the passageway section having an inner surface adapted to receive and hold said cartridge housing within the passageway section, and the mouthpiece, passageway section and cartridge communicating with each other; and
d) said other end of the passageway section includes a sharpened end around the periphery for penetrating said penetrable passageway barrier portions.

5. The cartridge of claim 4 in combination with a dispenser, said dispenser comprising:
(a) a molded plastic dispenser containing a number of compartments and a tray;
(b) said compartments are adapted to accommodate cartridges;
(c) said tray is adapted to accommodate a mouthpiece; and
(d) a sharpened tip, for penetrating the penetrable passageway barrier portions, is located at one end of the tray.

6. The cartridge of claim 1, wherein the nicotine reservoir comprises a porous polymer plug charged with nicotine free base.

7. The cartridge of claim 6, wherein the porous plug is formed of polyethylene.

8. The cartridge of claim 1, wherein said housing is formed of a copolymer of acrylonitrile and methyl acrylate.

9. The cartridge of claim 8 wherein the nicotine-impermeable barrier includes forming the passageway barrier portions of aluminum foil.

10. The cartridge of claim 9, wherein the aluminum foil includes a coating on at least one side of a copolymer of acrylonitrile and methyl acrylate with said coating being heat sealed to the housing.

11. The cartridge of claim 1, wherein said cartridge housing is covered with a layer of aluminum foil.

12. The cartridge of claim 11, wherein the aluminum foil includes a coating on at least one side of a copolymer of acrylonitrile and methyl acrylate with said coating being heat sealed to the housing.

13. The cartridge of claim 1, wherein said inert gas is nitrogen.

14. A nicotine delivery system with an extended shelf life, containing a measured amount of nicotine which can selectively be made accessible to a user, comprising:
(a) a container formed of a material which is effectively impermeable to nicotine and oxygen;
(b) a carrier in the container for carrying a measured amount of nicotine in a state which can supply nicotine in vapor form to a user, said carrier being maintained in the container in an effectively oxygen-free environment;
(c) access means for selectively providing the user with access to the interior of the container; and
(d) differential pressure means for allowing a differential pressure to be applied to the carrier for releasing nicotine in vapor form through said access means when the interior of the container is made accessible to the user.

15. The nicotine delivery system of claim 14, wherein the nicotine carrier comprises a porous polymer plug charged with a nicotine free-base.

16. The nicotine delivery system of claim 15, wherein the porous plug is formed of polyethylene.

17. The nicotine delivery system of claim 14, wherein said access means includes a selectively penetrable portion attached to the carrier by means of a nicotine-impermeable seal.

18. The nicotine delivery system of claim 14, wherein the container is tubular in shape and said access means and said differential pressure means includes penetrable seals at opposite ends of the container.

19. The nicotine delivery system of claim 14, wherein the container is formed at least in part of a polymer of acrylonitrile and methyl acrylate.

20. The nicotine delivery system of claim 19, wherein said access means is formed of an aluminum foil coated with a copolymer of acrylonitrile and methyl acrylate.

21. The nicotine delivery system of claim 20, wherein the coating of copolymer of acrylonitrile and methyl acrylate is heat sealed to the container.

22. The nicotine delivery system of claim 14, wherein the carrier is maintained in inert gas.

23. The nicotine delivery system of claim 22, wherein said inert gas is nitrogen.

* * * * *

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Our ref: 228784/OFRCPT

Your ref:

Date: 28 AUG 1996

Dear Sir

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Type Name:	Patent
Patent No.:	5167242
Base date:	01 DEC 1992
Proprietor:	PHARMACIA AB
Reference:	INH/PHA 0858
Client no.:	0748723
Annuity:	1
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U.S.A. Patent	5167242 1 01 JUN 1996	PHARMACIA AB Application No. 535967	US$990.00
U.S.A. Patent	5167252 1 01 JUN 1996	WR.GRACE+CO-CONN Application No. 647223	US$990.00
U.S.A. Patent	5167284 1 01 JUN 1996	CAMCO INTERNATIONAL INC. Application No. 732370	US$990.00
U.S.A. Patent	5167303 1 01 JUN 1996	TOKICO LTD. Application No. 07/688423	US$990.00
U.S.A. Patent	5167311 1 01 JUN 1996	ZEXEL CORP. Application No. 507354	US$990.00

US PT 5167234 1

US PT 5167242 1

US PT 5167252 1

US PT 5167284 1

US PT 5167303 1

US PT 5167311 1

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

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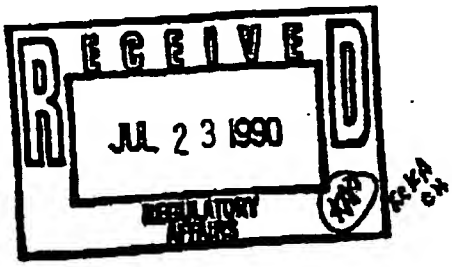

JUL 18 1990

IND 35,105

Pharmacia Inc.
800 Centennial Avenue
Piscataway, N.J. 08855
Attn: Karl A. Posselt

Dear :

We are pleased to acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 35,105

Sponsor: Pharmacia Inc.

Name of Drug: Nicotine Inhaler

Date of Submission: July 10, 1990

Date of Receipt: July 16, 1990

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until corrected, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is considered satisfactory.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder. Those responsibilities include reporting any unexpected fatal or life-threatening experiences by telephone to this Agency no later than three working days after receipt of the information (21 CFR 312.32) and the submission of annual progress reports.

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-007)
Attention: DOCUMENT CONTROL ROOM #98-23
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Corinne P. Moody

Project Manager
Center for Drug Evaluation and Research
(301) 443-3741

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-714

MAY 15 1996

Pharmacia Inc.
Post Office Box 16529
Columbus, Ohio 43216-6529

Attention: Barbara L. Gunther
Manager, Regulatory Affairs

Dear Ms. Gunther:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nicotrol Inhaler (nicotine inhalation system), 10 mg/unit

Therapeutic Classification: Standard

Date of Application: May 1, 1996

Date of Receipt: May 2, 1996

Our Reference Number: 20-714

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 1, 1996 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Bonnie McNeal
Consumer Safety Officer
Telephone: (301) 443-3741

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Corinne P. Moody

Corinne P. Moody
Acting Chief, Project Management Staff
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Rockville MD 20857

NDA 20-714

MAY 2 1997

Pharmacia and Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

Attention: Raymond E. Dann, Ph.D.
Director, OTC Regulatory Affairs

Dear Dr. Dann:

Please refer to your new drug application (NDA) dated May 1, 1996, received May 2, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nicotrol Inhaler (nicotine inhalation system), 10 mg/cartridge (4 mg delivered).

We acknowledge receipt of your submissions dated June 5, June 7, June 24, September 6, November 6, and December 5, 1996; January 13, January 29, March 7, March 20, March 24, March 26, April 7, April 15, April 24, April 29, April 30 and May 1, 1997. The User Fee goal date for this application is May 2, 1997.

This new drug application provides for a new nicotine replacement product as an aid to smoking cessation.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-714. Approval of this submission by FDA is not required before the labeling is used.

REGULATORY AFFAIRS
Received

MAY 0 8 1997

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated May 1, 1997. These commitments, along with any completion dates agreed upon, are listed below.

1. To modify the Inhaler mouthpiece and/or the product packaging to minimize the risk of pediatric poisoning from accidental ingestion, within 6-12 months after approval.

2. To track pediatric exposure to the Nicotrol Inhaler as reported to the American Association of Poison Control Centers.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Bonnie McNeal, Project Manager, at (301) 443-3741.

Sincerely,

Curtis Wright, M.D., M.P.H.
Acting Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

10

Facsimile - Transmission Record

TO: Beth Thielking

Company: Pharmacia
City: Kalamazoo
State: Michigan

Phone#: 616-833-8545

FAX#: 616-833-5612

FROM: Bonnie McNeal

Food and Drug Administration
HFD-170
Division of Anesthetic, Critical Care, and Addiction Drug Products
5600 Fishers Lane
Rockville, MD 20857
Phone#: 301-443-3741
Fax 301-443-7068
Date: September 24, 1997

Number of pages (including cover): 3

Telephone 301-443-4250 IMMEDIATELY if re-transmission is necessary.

Message:

Dear Beth,

Here is an approval letter for your supplement #1. We have agreed to await changes to the patient package insert and the carton labels until after you complete your testing.

Sincerely,

Bonnie

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-714/S-001

SEP 24 1997

Pharmacia & Upjohn Company
Pharmacia & Upjohn Consumer Healthcare
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Attention: Raymond E. Dann, Ph.D.
Director, OTC Regulatory Affairs

Dear Dr. Dann:

Please refer to your supplemental new drug application dated July 15, 1997, received July 15, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nicotrol Inhaler (nicotine inhalation system), 10 mg/cartridge (4 mg delivered).

We acknowledge receipt of your amendments dated July 15 and 23, 1997, August 5 and 12, 1997, and September 4, 1997.

The User Fee goal date for this application is January 15, 1998.

The supplemental application provides for a modified mouthpiece with a new supplier, and revised patient package insert.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

We also remind you to submit a supplement for revisions to the carton label and the patient package insert after you have finished the "senior friendliness" portion of your child resistant testing of the inhaler mouthpiece.

If you have any questions, please contact Bonnie McNeal, Project Manager, at (301) 443-3741.

Sincerely.

Albinus D'Sa, Ph.D.
Chemistry Team Leader (DNDC II)
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 5,167,242

Patentee: Turner et al. Attn: Box Patent Extension

Issue date: December 1, 1992

Attorney Docket No.: A89675US

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DECLARATION OF LARS NILSSON

Honorable Commissioner of Patents
and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

I, Lars Nilsson, a citizen of Sweden, do hereby declare that:

I am Vice President of Regulatory and Quality Affairs at Pharmacia & Upjohn Consumer Health Care, in Helsingborg, Sweden.

I have personal knowledge of all of the below listed events which occurred, from October 1990 to September 24, 1997, including the relevalt dates for the applicable regulatory period running from the date of submission of the IND on July 1, 1992, until final approval of the Nicotrol® Inhaler product on September 24, 1997.

ACTIVITIES DURING THE REGULATORY REVIEW PERIOD

Date	Activity
Study Period: Oct. 1990- Jan. 1992	Clinical study T90NI03 ongoing. Protocol May 1990. Report Feb. 1996
Study period: Nov. 1990 - Apr. 1992	Clinical study T90NI02 ongoing, Protocol Jun. 1990. Report Feb. 1996
Study period: Oct. 1990 - Nov. 1992	Clinical study T90NI01 ongoing. Protocol Jun. 1990. Report Feb. 1996
Study period: Sep. 1991 analytical test: Oct. - Nov. 1991	Pharmacokinetic study T91NI05, Report Dec. 1992
Study period: Oct. - Nov. 1991, analytical tests: Jan. - Feb. 1992	Pharmacokinetic study T91NI06, Prel. report Feb. 1992 Re-evaluation 1996. Report Jun. 1996
Study period: Oct. 1991 - Feb. 1992, analytical tests: May - Jun. 1992	Pharmacokinetic (pilot) study T91NI07, Report Nov. 1993
Study period: May - Jun. 1992, analytical tests: Aug. - Sep. 1992	Pharmacodynamic study 92NNIN004. Protocol Mar. 1992. Report Jul 1993
Jul. 1, 1992	**IND Submission**; Protocol 92NNIN002
Sep. 16, 1992	IND Submission; Protocol 92NNIN003
Study period: Sep. - Oct. 1992, analytical tests: Dec. 1992	Pharmacokinetic study 92NNIN005. Prel. report Dec. 1993. Re-evaluation 1994. Report Apr. 1995.
Nov. 16, 1992	Submission of Annual Report
Dec. 1, 1992	IND Submission; Protocol T91NI04

Study period: Oct. 1992-June 1994	Clinical study T91NI04 ongoing. Report Feb. 1996
Study period: May - Dec. 1993	Pharmacokinetic study 93NNIN007. Protocol Mar. 1993. Report Mar. 1994
Study period: Dec. 1994	Addendum to Pharmacokinetic study 93NNIN007. Protocol Sep. 1994. Report Jun. 1995
Study period: I: Feb. - Jun. 1995 and II: Mar. - Apr. 1996	Pharmacokinetic study 94 NNIN010, Protocol Dec. 1994. Report Feb. 1997 (I+II) (preliminary report Jan. 1996, I)
Study period: May - Jun. 1995, analytical tests: Jul. - Aug. 1995	Pharmacokinetic study 95NNIN011, Report Dec. 1995
Sep. - Oct. 1995	Pharmacokinetic study 95NNINI013, Report 1996 (Japan)
Re-evaluation: Dec. 1995- Jan. 1996	Report of re-evaluated pharmacokinetic pilot study T88NI02
1995 - Aug. 1996	Plans for and installation, qualification and validation of full scale production equipment and process
Jan. 1996 - Apr. 1996	Clinical summaries
Mar. 1996 - Apr. 1996	Compilation of NDA
May 1, 1996	**Submission of NDA**
Jun. 5, 1996	Submission of prototype mouthpiece
Jun. 13, 1996	Submission of requested documentation
Jun. 18, 1996	Telephone conference with the FDA
Jun. 24, 1996	Submission of requested data
Jul. 8, 1996	Questions from the FDA

Aug. 19, 1996	Submission of electronic versions of physician package insert and patient package insert August 19, 1996
Aug. 1996 to date	Plans for and installation, qualification and validation of new full scale production equipment
Sep. 6, 1996	Responses to questions of Jul. 8, 1996
Sep. 27, 1996	Submission of requested extra copies of clinical study reports
Oct. 31, 1996	Submission of Draft Advisory Committee Brochure
Nov. 6, 1996	Submission of publicly releasable version of Environmental Assessment Report
Nov. 8, 1996	Meeting with the FDA to finalize the Advisory Committee Brochure
Nov. 15, 1996	Submission of background material for the Nicotrol Inhaler Drug Abuse Advisory
Nov. 22, 1996	Request for more information
Dec. 5, 1996	Submission of NDA Amendment
Dec. 13, 1997	DAAC (Drug Abuse Advisory Committee) meeting with FDA
Jan. 13, 1997	Submission of responses to FDA's questions
Jan. 29, 1997	Supplemental responses
Feb. 7, 1997	Methods Validation Package to FDA laboratories
Mar. 6, 1997	Questions from the FDA
Mar. 7, 1997	Submission of NDA Amendment
March 10, 1997	Submission of revised methods

	to FDA laboratories
Mar. 20, 1997	Submission of Revised Draft labelling
Mar. 24, 1997	Submission of Responses
Mar. 26, 1997	Revised patient information leaflet
Mar. 31, 1997	Submission of requested analytical equipment to FDA laboratories
April 4, 1997	Submission of requested analytical equipment to FDA laboratories
Apr. 7, 1997	Responses to questions submission of requested document clinical study report
Apr. 15, 1997	Submission of Development plan
Apr. 24, 1997	Revised draft label
May 1, 1997	Submission of Phase IV Commitments
May 2, 1997	Letter from FDA
May 5, 1997	Submission of requested additional samples to FDA
May 5 - July 15, 1997	Ongoing development of child resistant mouthpiece and minor corrections of appearance
July 15, 1997	Submission of supplemental information
July 23, 1997	Response to FDA request of July 15, 1997
September 4, 1997	Submission of child resistant test results to FDA
September 4, 1997	Submission of responses to questions
September 24, 1997	**FDA final approval letter**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issued thereon.

21 Nov. 1997
Date

Lars Nilsson

nilsson.dec/ynq